

Synthesis and properties of hydrazones bearing amide, thioamide and amidine functions

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Abstract

This review provides detailed methods for the synthesis, structures and chemical properties of hydrazones bearing carboxamide, thioamide and amidine functions. The main accent was put on the cyclization reactions leading to pyrazoles, thiazoles, 1,2,3-triazoles, 1,2,3-thiadiazoles, 1,2,4-triazines and other heterocyclic compounds. In addition, we have reviewed methods for the synthesis of substrates for pericyclic reactions from the hydrazones.

Keywords: Hydrazone, carboxamide, thioamide, amidines, cyclization

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Introduction

Hydrazones and their derivatives constitute a versatile class of compounds in organic chemistry. These compounds have interesting biological properties, such as anti-inflammatory, analgesic, anticonvulsant, antituberculous, antitumor, anti-HIV and antimicrobial activity.¹ Hydrazones are important compounds for drug design, as possible ligands for metal complexes, organocatalysis and also for the syntheses of heterocyclic compounds.² The ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity are all desirable characteristics of hydrazones. Due to these positive traits, hydrazones have been under study for a long time, but much of their basic chemistry remains unexplored.

Hydrazones contain two connected nitrogen atoms of different nature and a C-N double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structural fragments are mainly responsible for the physical and chemical properties of hydrazones (Figure 1). Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino type nitrogen is more reactive. The carbon atom of hydrazone group has both electrophilic and nucleophilic character.³

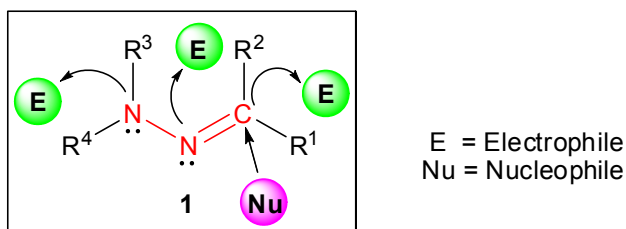
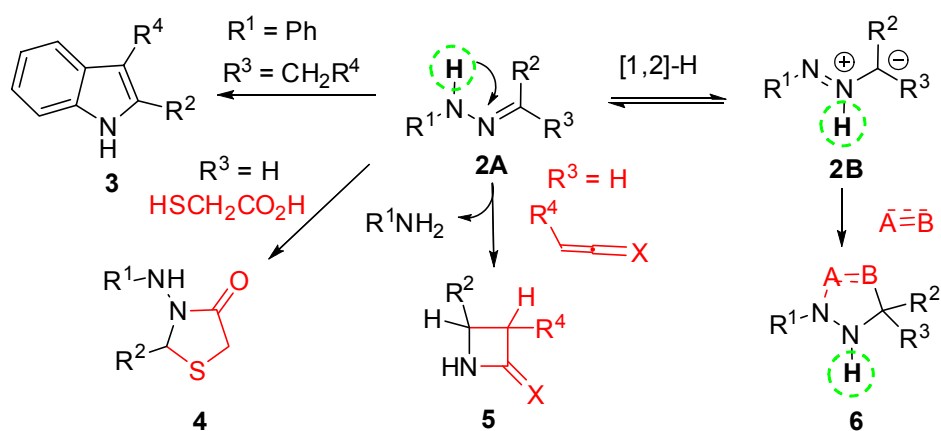


Figure 1. Classification of active centers.

Due to the capability to react with electrophilic and nucleophilic reagents, hydrazones are widely used in organic synthesis, especially for the preparation of heterocyclic compounds. It is worth mentioning the synthesis of indoles **3** according to the Fischer reaction,^{3a} the synthesis of 4-thiazolidin-4-ones **4**,^{1a} the synthesis of azetidines **5**⁴ by [2+2] cycloaddition and different syntheses of various five-membered heterocyclic compounds **6** by 1,3-dipolar cycloaddition of azomethine imines⁵ that are formed by a 1,2-*H*-shift as depicted in the Scheme 1.



Scheme 1

The introduction of functional groups in the hydrazone molecules expands the scope of use of the latter in organic synthesis. Moreover, the combination of the hydrazone group with other functional groups leads to compounds with unique physical and chemical properties. Hydrazones containing a halo atom in α - or β -positions have been explored for many years as ways to generate nitrile imines⁶ and 1,2-diaza-1,3-butadienes⁷ that are active intermediates in cycloaddition chemistry. The amidrazones and thiosemicarbazones are well documented because of their biological activity and use in the synthesis of heterocyclic compounds.^{3a,8} Synthetic approaches and chemical reactivity of the hydrazones substituted with ester and cyano groups were first reported in 1894 but new findings were continuously added, some only recently.⁹ We are reporting here a review on the synthesis, spectral and chemical properties of hydrazones of type **7** containing amide, thioamide and amidine groups (Figure 2). The structure **8** represents a special case where these groups are incorporated into a ring.

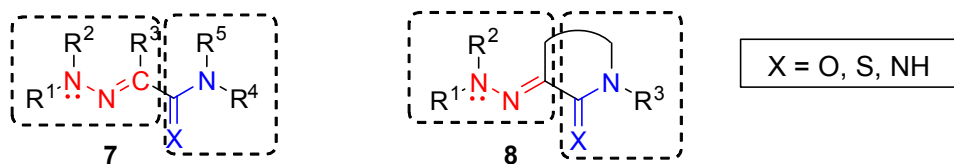


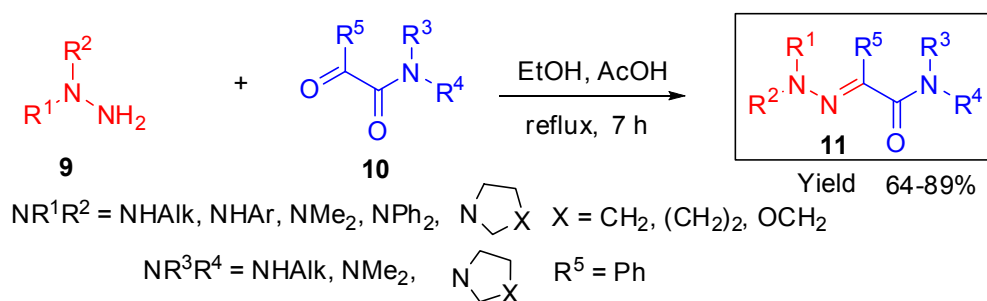
Figure 2. Structures of hydrazones with amide, thioamide and amidine groups

2. Syntheses of hydrazono-amides, -thioamides and –amidines

2.1 Condensation reaction of hydrazines with carbonyl compounds

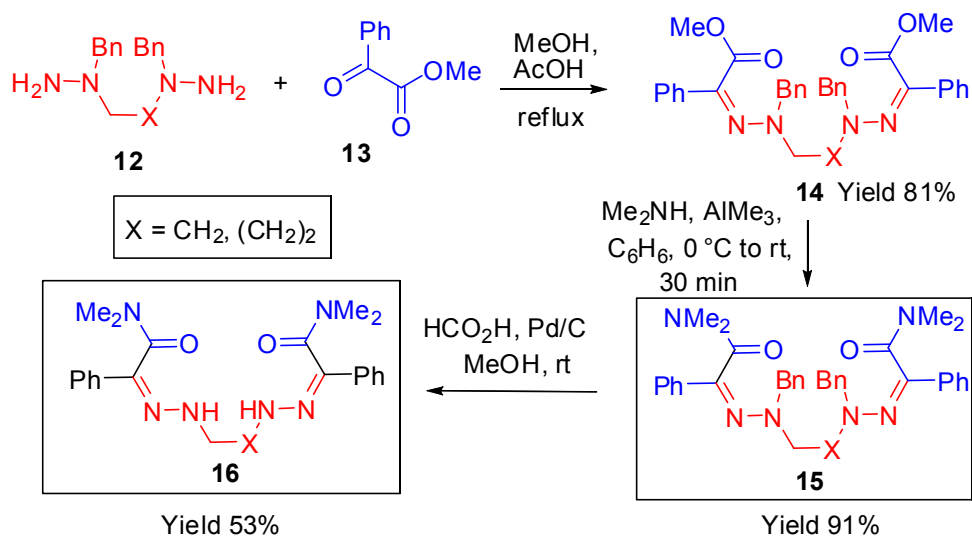
The most general and oldest method for the synthesis of hydrazones is the reaction of hydrazines with carbonyl compounds.^{3,10} Because of the high nucleophilicity of both hydrazine nitrogen atoms the use of this method is difficult for the preparation of hydrazones bearing carbonyl and other electrophilic substituents. In fact, hydrazones bearing thioamide and amidine moieties are not available by this method at all.

The amide group is less reactive than the ester and ketone functions. Therefore, amido-hydrazones **11** may be selectively prepared by reaction of alkyl- or arylhydrazines **9** with 2-oxo-2-phenylacetamides **10** (Scheme 2).¹¹



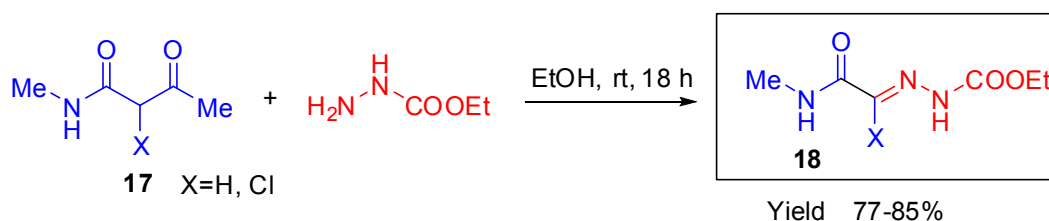
Scheme 2

The use of the benzyl protecting group allowed the authors^{11f,g} to obtain the *bis*-hydrazones **15** and **16**. The first stage of the method is the condensation of the dihydrazines **12**, where two nitrogen atoms are protected by benzyl groups, with two equivalents of methyl benzoylformate **13**. Then bis(hydrazonoester) **14** was transformed into the bis(hydrazonoamide) **15** by the action of dimethylaluminium dimethylamide formed *in situ* by addition of dimethylamine to trimethylaluminium (Scheme 3). The benzyl groups were removed by hydrogenolysis at the last step.



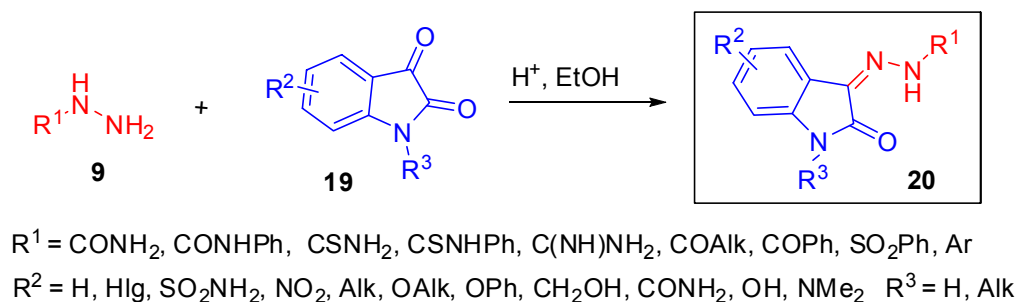
Scheme 3

It is interesting to note that the reaction of N-methyl- α -chloroacetoacetamide **17** with ethyl carbazate in ethanol affords N-acylhydrazones **18** as the only product. The expected substitution of chlorine atom was not observed (Scheme 4).¹²



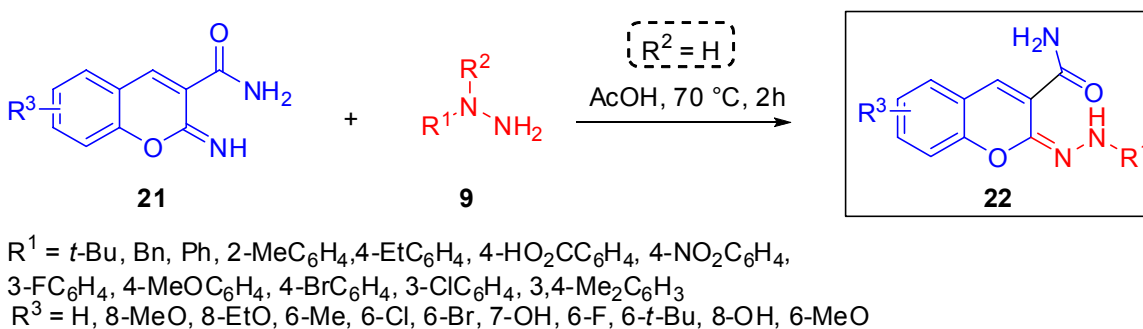
Scheme 4

Since indole derivatives exhibit interesting biological properties, a series of hydrazones **20** bearing an amide group incorporated into an indole moiety were prepared by reactions of isatines **19** with hydrazines **9** ($\text{R}^2 = \text{H}$).¹³ Compounds **20** ($\text{R}^1 = 4\text{-SO}_2\text{NH}_2\text{C}_6\text{H}_4$) represent a novel class of CDK2 (cyclin-dependent kinase 2) inhibitor (Scheme 5). Members of this series of inhibitors cause an arrest of the cell cycle and exhibit a selective killing effect on several tumor cell lines.^{13a} Hydrazones of angular isatines were synthesized to check their antiviral activity.^{13b} Compounds **20** with an acylhydrazono group prepared by this reaction exhibited the inhibition of cannabinoid receptors 2.^{13c,d}



Scheme 5

The synthesis of 2-hydrazonocoumarines **22** was carried out based on the reaction of imine **21** with alkyl-, benzyl-, and arylhydrazines **9** (Scheme 6).¹⁴

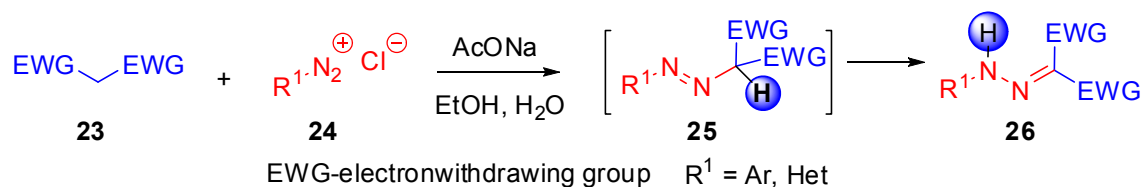


Scheme 6

To improve this protocol, microwave-assisted organic synthesis was used. Under these conditions, a full conversion of the starting imines **21** into the desired 2-hydrazono-2*H*-chromenes **22** took place in a reduced (2 h to 2 min) reaction time.¹⁴

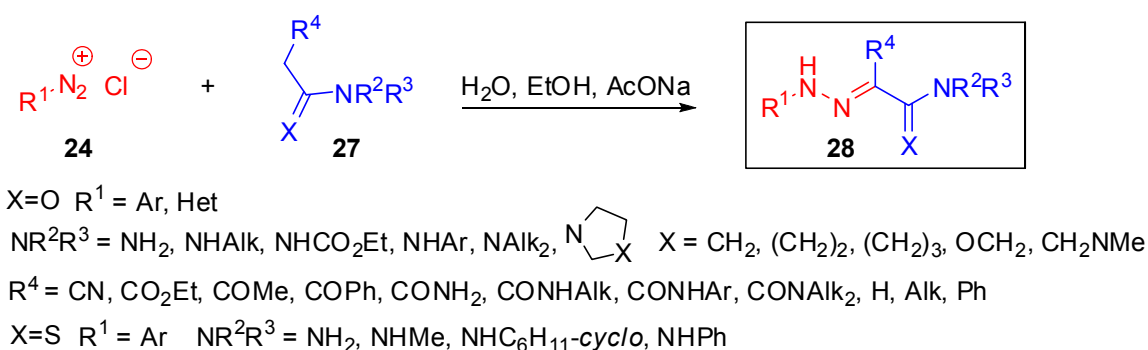
2.2 Coupling of diazonium salts with active methylene compounds

The coupling of diazonium compounds with active methylene compounds is one of the oldest methods for the synthesis of arylhydrazones.^{3,10,15} In a typical reaction between compounds **23**, containing two electron-withdrawing groups, with aryl(hetaryl)diazonium chloride **24** an unstable azo intermediate **25** is considered to form, which spontaneously tautomerizes into the hydrazone **26** (Scheme 7). The reaction is usually carried out in a cold aqueous solution buffered with sodium acetate, but the pH of the medium can be lowered for strongly activated methylene compounds.



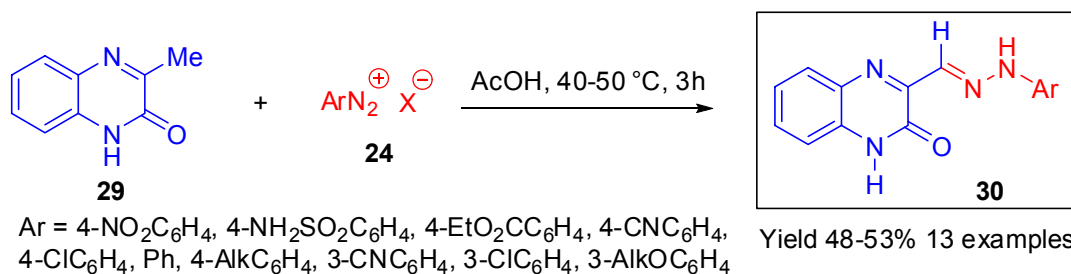
Scheme 7

There are many papers published in the literature where a large variety of compounds of type **27** were involved in the reaction. Thus, arylhydrazonoacetamides **28** ($\text{X}=\text{O}$)¹⁶ and thioamides ($\text{X}=\text{S}$)¹⁷ with various substituents R^1 - R^4 were prepared by the method (Scheme 8).



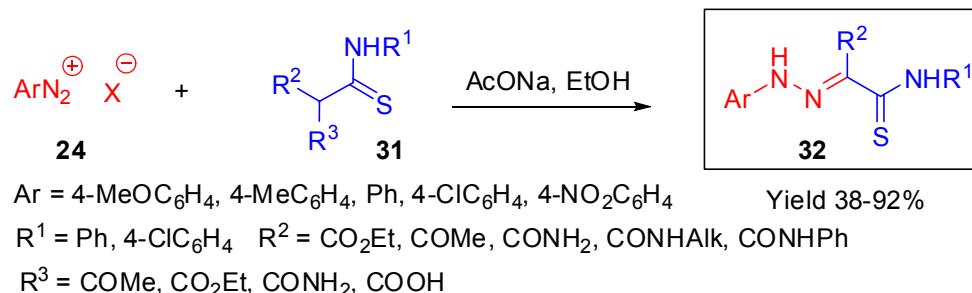
Scheme 8

Interestingly, 3-methyl-2-oxo-1,2-dihydroquinoxaline **29** can react with benzenediazonium salts **24** ($\text{R}^1=\text{Ar}$) at relatively elevated temperature to give 3-(arylhazono)methyl-2-oxo-1,2-dihydroquinoxalines **30**.¹⁸ In this case, the methyl group takes part in the azo-coupling reaction (Scheme 9).



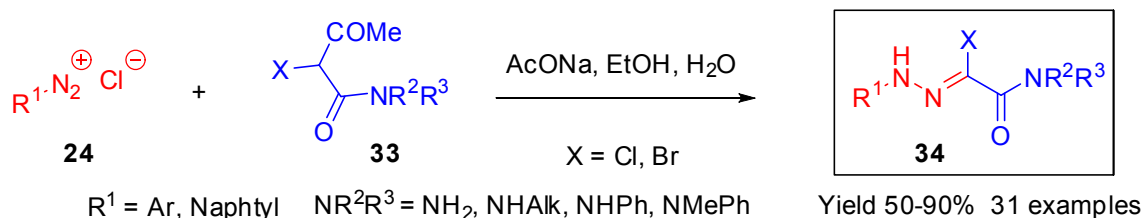
Scheme 9

A series of arylhydrazonothioacetanilides **32** were prepared by the Japp-Klingemann reaction, which is an azo coupling accompanied by the elimination of one of the two electron-withdrawing groups such as COOH , COMe , CONH_2 and COOEt (Scheme 10).¹⁹



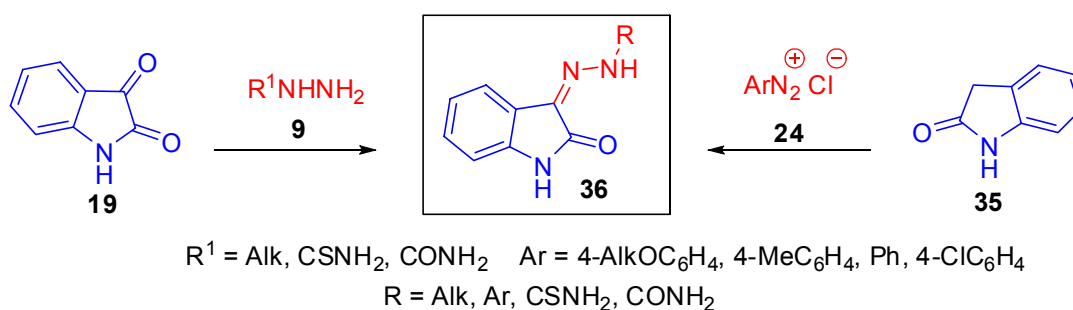
Scheme 10

The use of Japp-Klingemann reaction is also a convenient method for the synthesis of hydrazoneacetamides **34** bearing halogen atom (Scheme 11).^{16g,20}



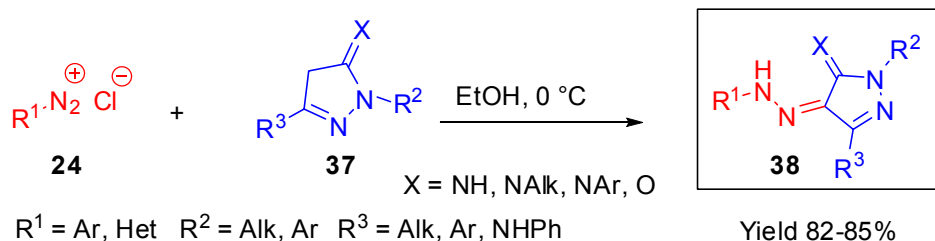
Scheme 11

Isatine hydrazones **36** were prepared either by condensation of isatine with hydrazines **9** or by the alternative process of azo coupling of aryldiazonium salts **24** with indole-2-one **35** (Scheme 12).²¹ The combination of two methods allowed to prepare a library of hydrazones **36** where R includes aryl, alkyl, carbamoyl and thiocarbamoyl moieties.



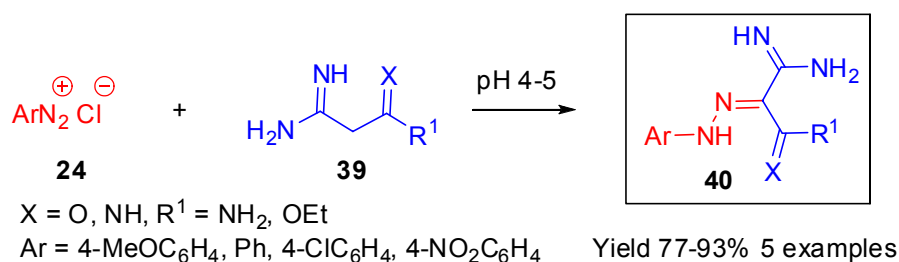
Scheme 12

The azo coupling reaction is also used to prepare 4-arylhydrazonopyrazol-5-ones and -imines **38** (Scheme 13).²²



Scheme 13

The coupling of aryldiazonium chloride **24** ($R^1=Ar$) with malonamidines **39** was used to prepare arylhydrazonomalonamidines **40** (Scheme 14).²³



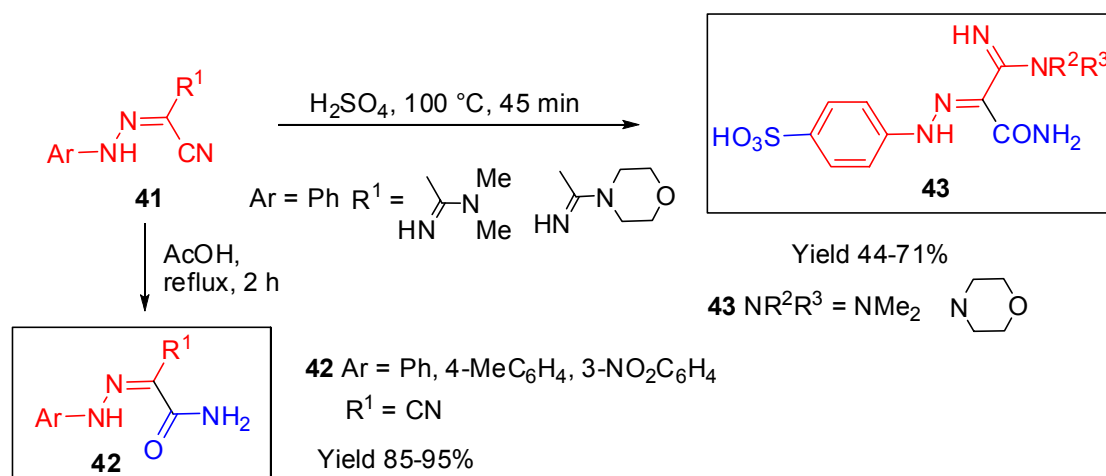
Scheme 14

These compounds are not stable and partial decomposition during the preparation takes place. To prepare these compounds one should keep the pH of medium well within the narrow interval of 4-5.^{23a-c}

It is worth noting that the synthetic method for hydrazones by the azo coupling reaction is more suitable to prepare compounds bearing carbamoyl, thiocarbamoyl and amidine groups than the alternative method based on the reaction of carbonyl compounds with hydrazines.

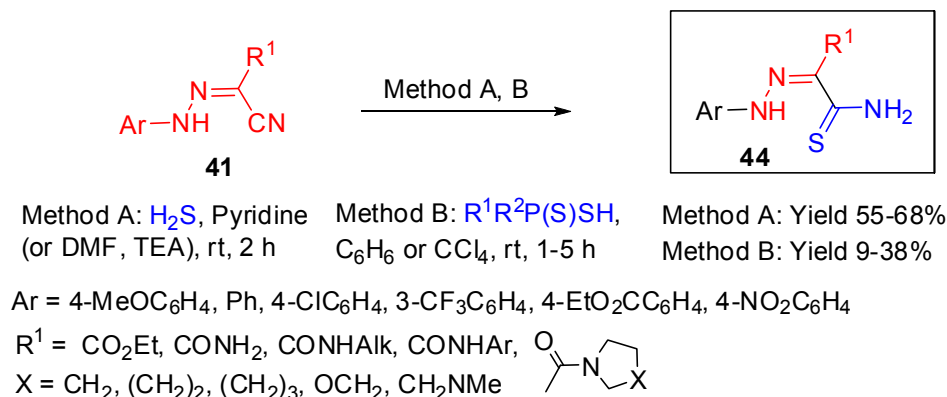
2.3 Synthesis of hydrazones by modification of the substituents

Hydrazono-amides **42**, **43** can be prepared by reaction of hydrazono-esters with amines or by hydrolysis of a cyano group of hydrazonomalononitriles (Scheme 15).^{16l,24} The reaction in sulfuric acid accompanied by sulfonation to give final compounds **43**. These reactions are not widely used in organic synthesis because of the availability of hydrazono-amides by other methods.



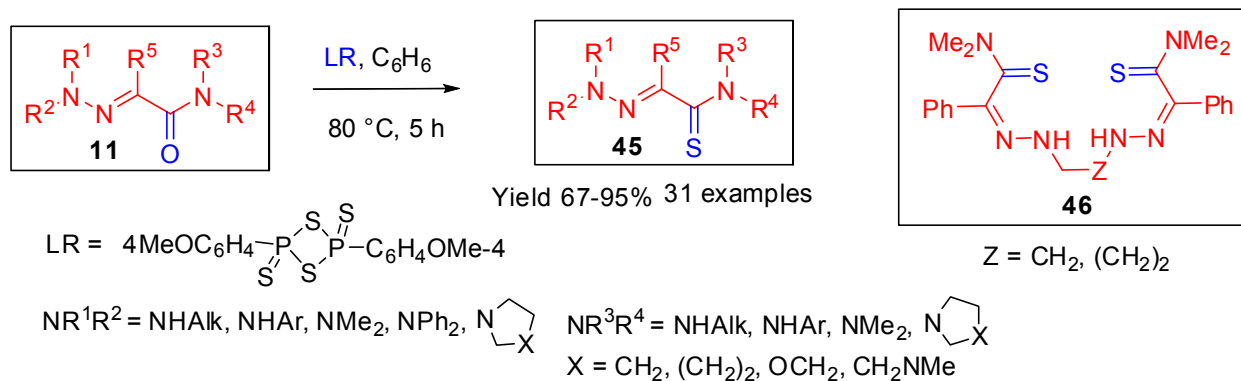
Scheme 15

A large series of 2-hydrazonothioacetamides **44** were obtained by reaction of nitriles **41** either with hydrogen sulfide in basic solutions or by treatment with dialkylphosphinodithioic acids (Scheme 16).^{16j,25}



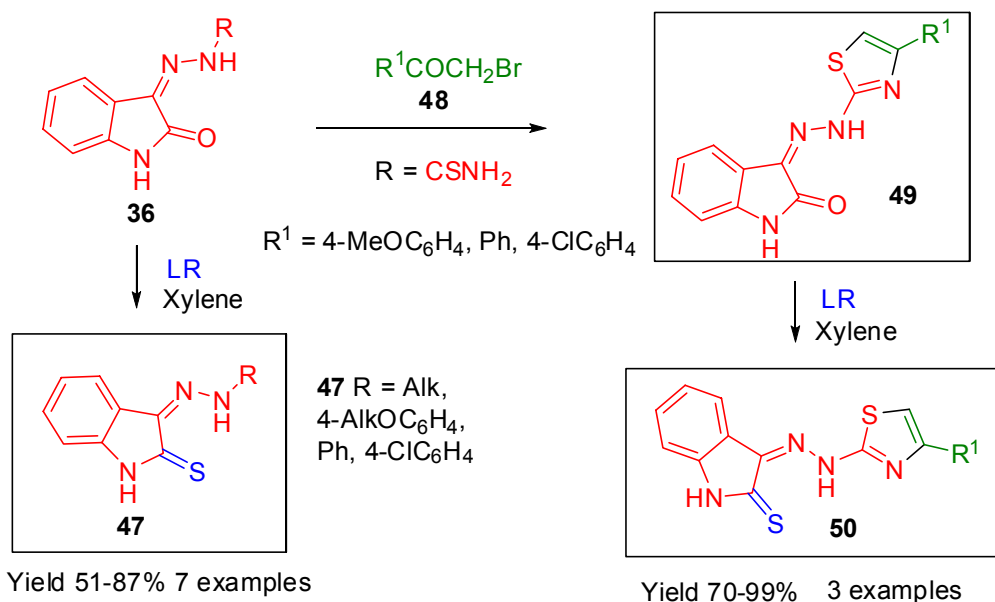
Scheme 16

Reaction of hydrazono-amides with Lawesson's reagent represents an alternative method to prepare thioamides **45** (Scheme 17).^{11a-e,26} Tetradentate *bis*-hydrazones **46** were prepared successfully in a similar way.^{11f-g}



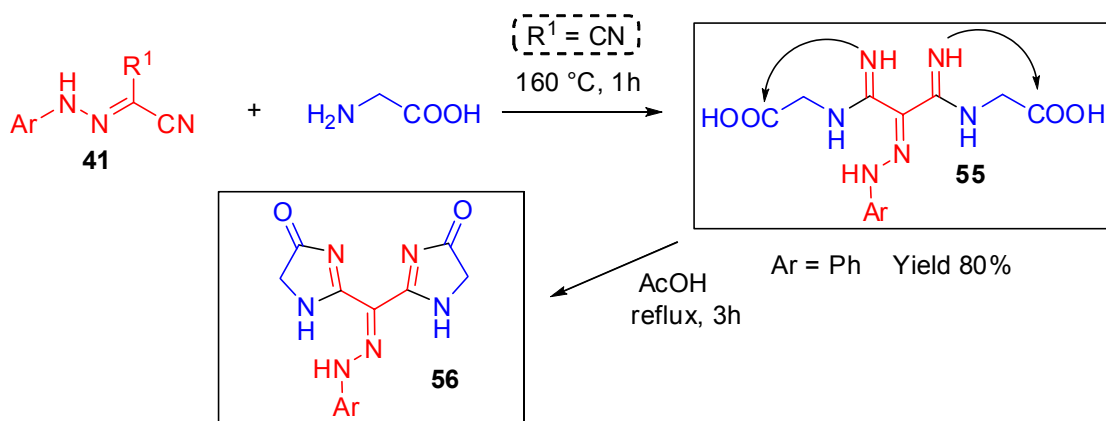
Scheme 17

Hydrazone **36** has been shown to react with Lawesson's reagent to form 3-hydrazono-2-thioindole **47** (Scheme 18). Furthermore, the product of the reaction of compound **36** (R¹=CSNH₂) with bromoacetophenones **48**, namely amide **49** is also capable of reacting with Lawesson's reagent to form indole-2-thione **50**.²¹



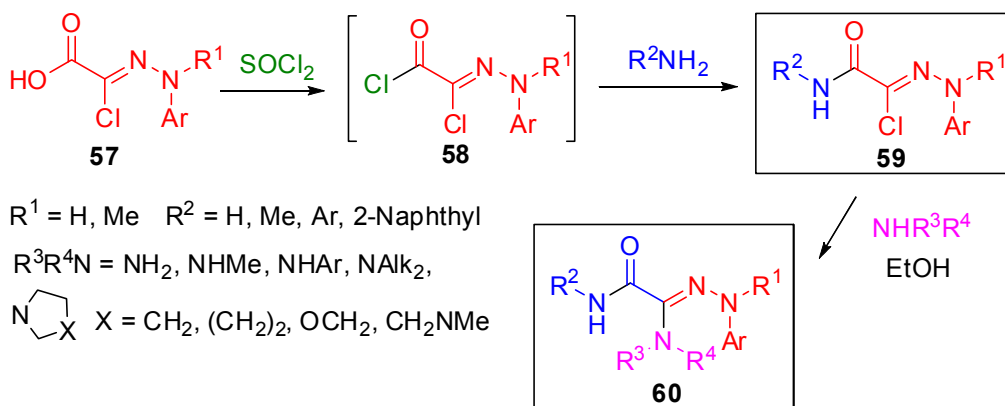
Scheme 18

3-Hydrazonopyrazole-2-thione **52** was prepared by both thionation of amide **38** with Lawesson's reagent and by a two step synthesis *via* chlorination of **38** with phosphorus pentachloride followed by substitution of chlorine to the thione function by reaction with sodium sulfide (Scheme19).^{22c,d}



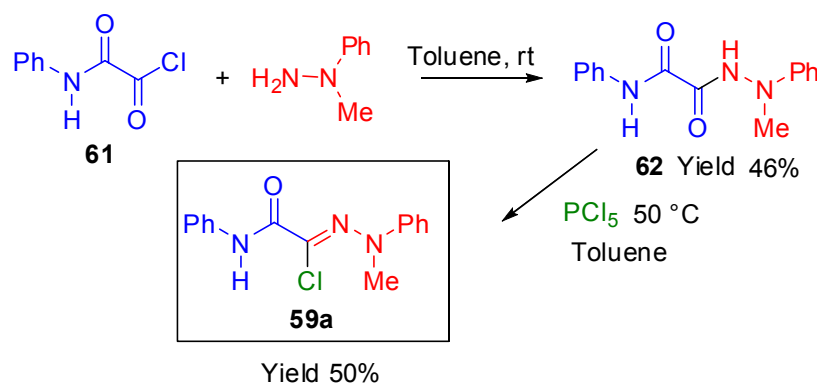
Scheme 21

2-Chloro-2-aryldihydropyrimidin-4(1H)-ones **59** can be prepared by the reaction of acid **57** with thionyl chloride followed by substitution with amines (Scheme 22).^{20b} In a second stage, the chlorine of chlorohydrazone **59** can be substituted by the amino moiety as a result of its reaction with various amines to form 2-amino-2-aryldihydropyrimidin-4(1H)-ones **60** exhibiting interesting biological properties.^{20b,28}



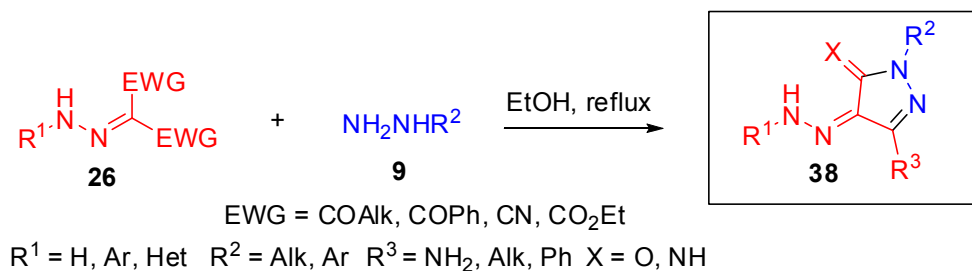
Scheme 22

2-Oxo-2-(phenylamino)acetohydrazonoyl chloride **59a** was produced by the reaction of 2-oxo-2-(phenylamino)acetyl chloride **61** with N-methyl-N-phenylhydrazine followed by treatment of the intermediate hydrazide **62** with phosphorus pentachloride in toluene to form the final product (Scheme 23).^{28a}



Scheme 23

4-Arylhydrazono-1*H*-pyrazoles can be easily prepared by the reaction of arylhydrazonomalononitrile,²⁹ - arylhydrazonocyanoacetate,³⁰ arylhydrazonoacetoacetate³¹ and arylhydrazono-3-ketiminobutyronitriles³² with hydrazine (Scheme 24). Depending on the type of EWG, 3-amino-, 3-oxo- and 3-methylpyrazoles **38** can be prepared by this method.



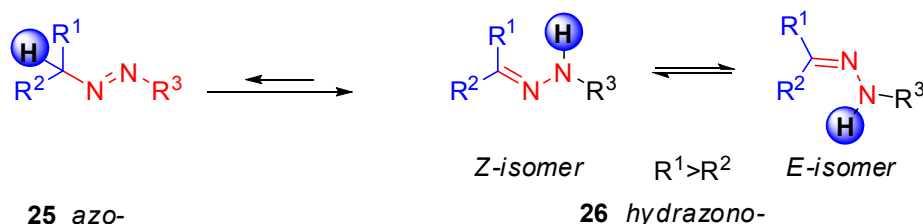
Scheme 24

Indeed, reactions of carbonyl compounds with hydrazines, coupling of diazonium salts with malonamides, malonthioamides and malonamidines and elaboration of preformed hydrazones constitute an arsenal of synthetic methods to hydrazones containing amide, thioamide and amidine groups.

3. Structure of hydrazonoamides -thioamides and -amidines

The hydrazono-amide, -thioamide, and -amidine molecules contain a π -system of two double bonds and an NH-fragment that provides the basis for the azo-hydrazone tautomerism and *Z,E*-stereoisomerism. The lone electron pairs of the heteroatoms and the NH-bonds can form hydrogen bonds and may stabilize both tautomer forms and stereoisomers. This section contain data on the azo-hydrazone tautomerism, the *Z,E* stereoisomerism and the hydrogen bonds.

The azo-hydrazone tautomerism has been investigated by numerous workers with a view to prove the existence of an equilibrium, to investigate the influence of substituents, solvents, temperature and to gain an understanding on the (non)existence of this thermodynamic equilibrium.³³ These investigations have been conducted by a combination of spectroscopic (IR, UV, NMR ^1H , ^{13}C , ^{15}N) and computational methods and they have shown the existence of most compounds in the form of hydrazones rather than azo compounds (Scheme 25).^{3,9,11b,13a,16i,16m,21,22a}



Scheme 25

3.1 Hydrazone-amides

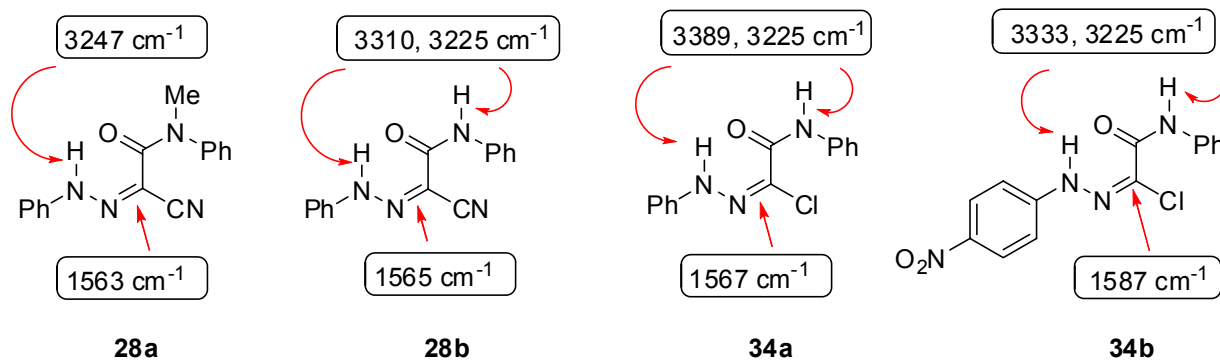
The study of the fine structure of hydrazones by various spectral methods and by single crystal X-ray diffraction analysis has focused in major part on 2-hydrazoneacetamides. This is explained by the wide availability of many derivatives of this series and with their importance as pigments and biologically active compounds.^{28,33}

The absorption pattern in the UV region for hydrazone-amides substituted by keto-, cyano-, amino groups and by chlorine was in each case characterized by the presence of three bands. The first one is located in the range of 390-350 nm; the second band is located in the 290-250 nm region and the third one is below 240 nm.^{16g-i,m,28a} The introduction of electron-acceptor substituents to arylhydrazonoyl fragment was shown to lead to a bathochromic shift of the first band.^{16m}

UV spectra of azo compounds are characterized by an intensive wave maximum at 270-280 nm. In contrast to azo compounds, a weak absorption band (or no band) for hydrazones is located at 284 to 295 nm and a strong absorption band is observed at 390-320 nm, which distinguishes these two types of compounds.³⁴ It is worth noting that this absorption is shifted to higher wavelength in the case of the *E*-isomer in comparison with the *Z*-isomer, possibly due to the different hydrogen bonding in both isomers.^{28c}

Indeed the data of UV spectra are rather in accordance with the hydrazone than with the azo structure.

The IR spectra of hydrazone-amides also confirm their structures as hydrazones. The IR spectra of hydrazone-amides contain an NH bond stretching at 3500-3100 cm^{-1} corresponding to amide and hydrazone groups, three bands in the region of 1700-1500 cm^{-1} of C=O bond (1690-1670 cm^{-1}), aromatic C=C bonds (1600 cm^{-1}), and C=N bond (1560-1570 cm^{-1}) (Scheme 26).^{16g-i,m,28}

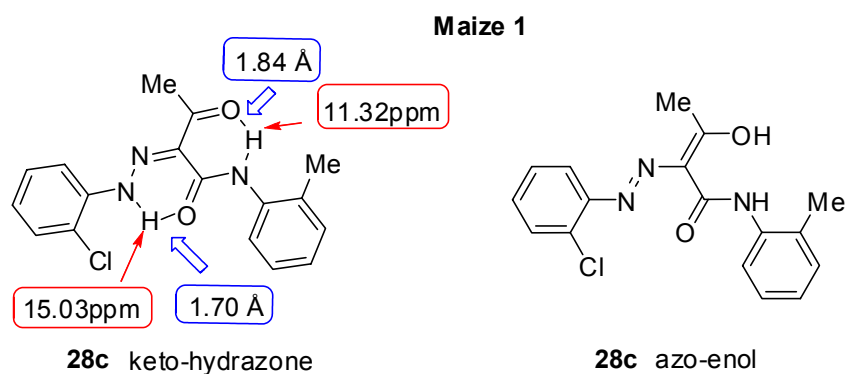


Scheme 26

The presence of a C=N bond in the molecules affects the position of the CN stretching, shifting it to 2220 cm^{-1} . A shift of the CO bond stretching to lower wavenumber has been observed in the IR spectra of hydrazones **28**, **34** due to both conjugation with C=N bond and formation of a hydrogen bond with the carbonyl group.^{16h}

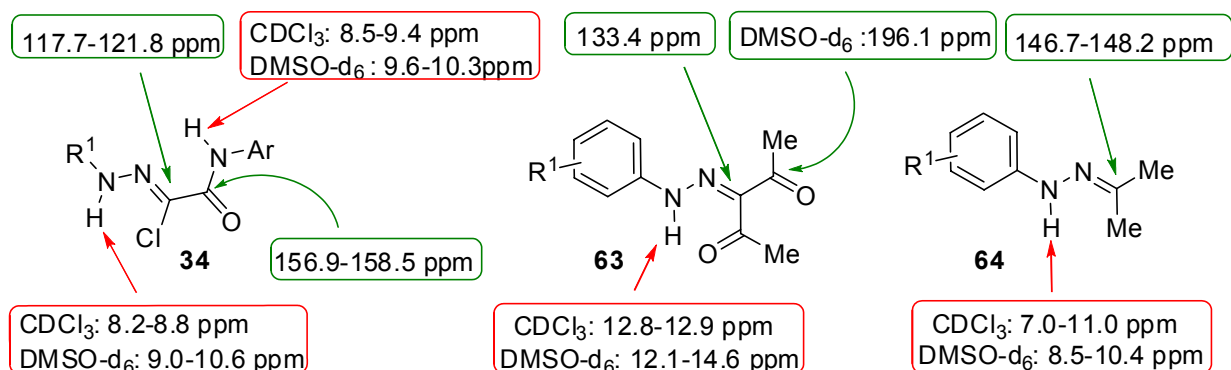
The ^1H , ^{13}C and ^{15}N NMR spectroscopic techniques and an X-ray diffraction of single crystals are much more informative tools for the study of the fine structure of hydrazono-amides including information on *Z,E*-isomerism and hydrogen bonding.

The presence of a signal in the ^1H NMR spectra in the region of 8-15 ppm gives evidence of the presence of an ArNH fragment and confirms the hydrazone structure. Furthermore, the downfield shift of this signal is characteristic for the formation of an intramolecular hydrogen bond of the NH proton. The amide proton ($-\text{NH}-\text{C}=\text{O}$) is found back as a singlet at δ 10.98-11.16, and the hydrazone proton ($>\text{C}=\text{N}-\text{NH}$) shows a singlet at δ 13.90-14.32.^{3,33b} The strongest hydrogen bonds are presented in the amides of 2-hydrazonoacetoacetic acid **28** ($\text{X}=\text{O}$, $\text{R}^4=\text{Ac}$). For this type of compounds, one can propose keto-hydrazone and azo-enol tautomer forms. The X-ray analysis of azo-pigment **Maize 1** (**28c**) allows to rule out the azo-enol form **28c** from consideration for crystalline state (Scheme 27).^{33a}



Scheme 27

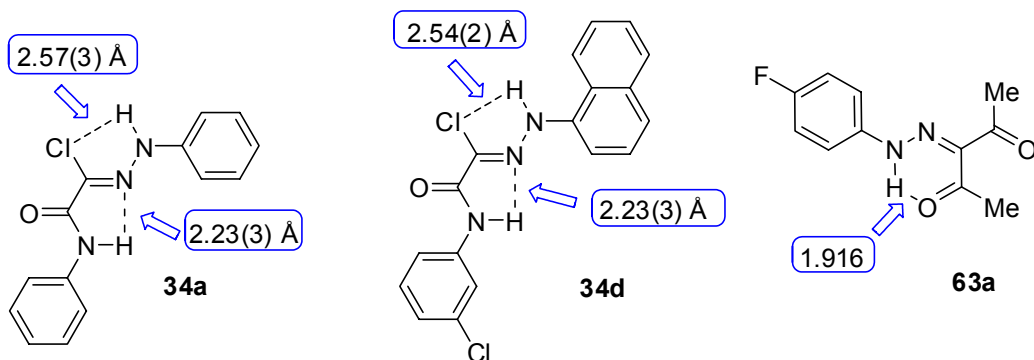
The signals of the $\text{NHN}=\text{C}$ proton of hydrazoneyl chlorides **34** ($\text{X}=\text{Cl}$, $\text{R}^1=\text{Ar}$, $\text{NR}^2\text{R}^3=\text{NHAr}$) in the ^1H NMR spectra are upfield shifted in comparison with ketone hydrazones **63** and are slightly down shifted in comparison with arylhydrazone of acetone **64** (Scheme 28).^{28a,35}



Scheme 28

Similar to the trends seen in the ^1H NMR spectra, the signal of iminyl carbon of hydrazoneyl chlorides **34** in the ^{13}C NMR spectra is upfield shifted for more than 25 ppm in comparison with acetone *N*-phenylhydrazones **64** and for 15 ppm in comparison with 2-arylhydrazonoacetoacetates **63** (Scheme 28).^{3,35}

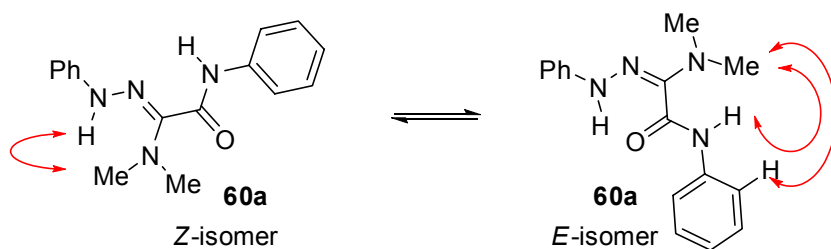
The data of single crystal X-ray diffraction of arylhydrazoneyl chloride **34** show the coplanarity of the amide and the hydrazone fragments with a deviation from planarity of only $7-9^\circ$ (Scheme 29). Two intramolecular hydrogen bonds N-H-Cl and N-H-N are present in the molecule as shown in Scheme 29. Both compounds, as shown by X-ray analysis, are *Z*-configured.^{28a}



Scheme 29

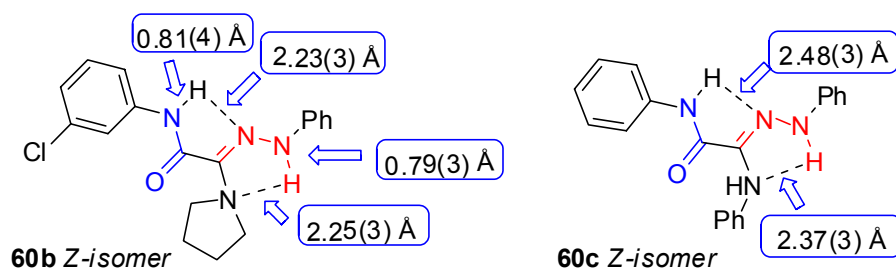
NMR spectra of amidrazones of type **60** (Scheme 22) are rather complex and often contain sets of signals for protons of various isomers. The introduction of an amino group leads to the

possibility of formation of new hydrogen bonds, that can stabilize stereoisomers with various positions of carbonyl and C=N bonds of the hydrazone group. Crude products of different reaction mixtures were investigated by ^1H NMR spectroscopy. It could be observed that the mixture contained variable amounts of *E*-isomers but always less than 50%. NOE experiments with compound **60a** ($\text{R}^1=\text{Ph}$, $\text{R}^2=\text{Ph}$, $\text{NR}^3\text{R}^4=\text{NMe}_2$) revealed that it exists as a mixture of *Z*- and *E*-isomers (Scheme 30) where the *Z*-isomer is the major product.^{28c}



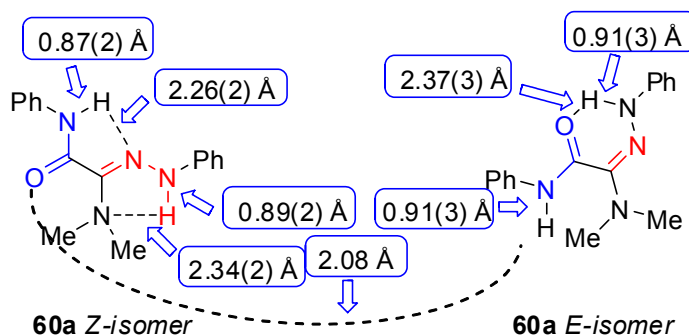
Scheme 30

In some cases, *Z*- and *E*-isomers of hydrazones **60** could be separated from the crude products by fractional crystallization or column chromatography. X-ray diffraction analysis of the hydrazones **60b,c** confirmed that these compounds are *Z*-configured (Scheme 31).^{28c}



Scheme 31

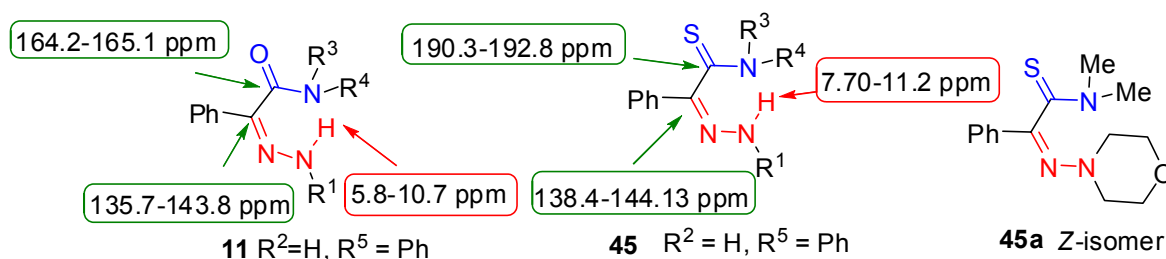
Unfortunately, all efforts to get crystals of *E*-isomers **60a** resulted in the isolation of crystals of an *E/Z*-isomer mixture in ratio 1:1 (Scheme 32).^{28c}



Scheme 32

Similar to **Z-60b,c**, that is stabilized by two intramolecular hydrogen bonds (Scheme 31), **E-60a** has also two hydrogen bonds one of them is between the carbonyl oxygen atom and the NH of the hydrazono group and another one between the NH of the amide fragment and the oxygen atom of the carbonyl group of the *Z/E*-isomer **60a** as shown in Scheme 32.

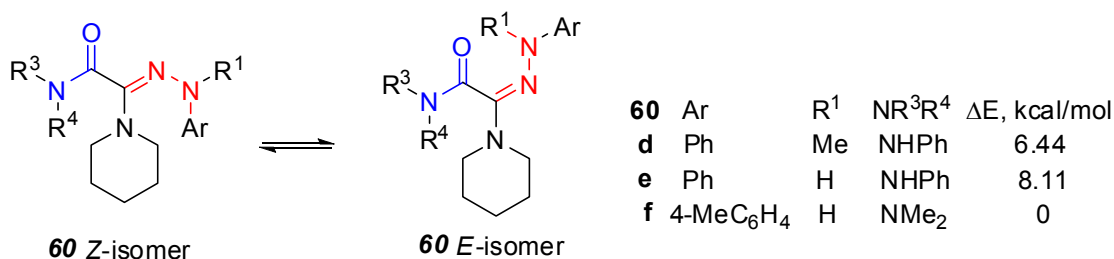
The formation of two intramolecular hydrogen bonds is confirmed by the shift of signals for the amide NH proton and of the carbon signal the C=N-NHAr group of **Z-60** that is upfield shifted in comparison with the *E*-isomer. On the contrary the proton signal of the hydrazono group is downfield shifted (Scheme 33).^{28c}



Scheme 33

Ab initio calculations, carried out at the RHF/6-31G* level^{28c} demonstrated that the *Z*-isomers of compounds **60** containing either dimethylamino or morpholino groups at position 2 are thermodynamically more stable than the *E*-isomers. The energy differences between the *Z*- and *E*-isomers range between 1.411 kcal/mol.

On the other hand, F. Krauth *et al.*^{28d} calculated the energy of *Z*-, and *E*-isomers for hydrazones **60** bearing a piperidine ring at position 2 by the B3LYP/6-31G(d) method and confirmed the higher stability of *E*-isomer for compounds **60d,e** and equal stability for the isomers of **60f** (Scheme 34).



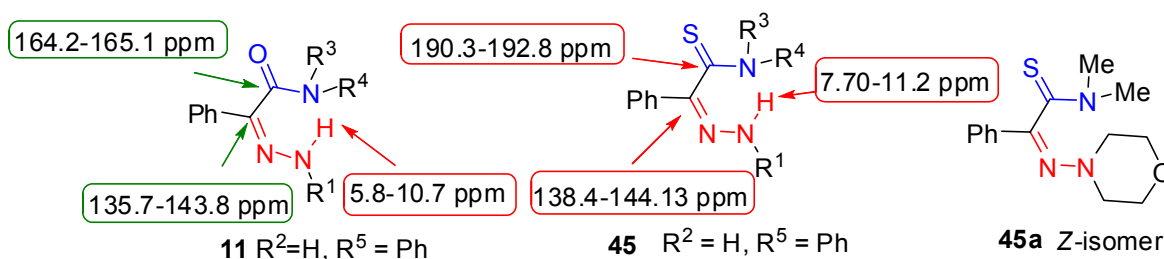
Scheme 34

It is worth noting that intra- and intermolecular hydrogen bond interactions, which are identified in solid state of compounds **60** (Scheme 30-33), may not be present in polar solvents. All compounds were found to form *E/Z*-equilibrium in solution.²⁸

3.2 Hydrazone-thioamides

The fine structure of hydrazone-thioamides has been studied to a lesser extent as hydrazone-amides. As the rule, authors publish limited data sufficient to identify the common structure and purity of prepared compounds.

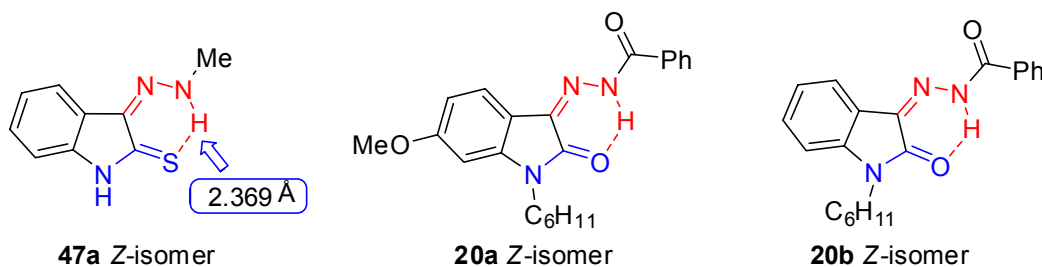
The study of the NMR spectra of thioamides **45** shows that the NH proton signals and the carbon signals of the C=N-NH fragment are downfield shifted in comparison with amide **11** as shown in Scheme 35. Single crystal X-ray diffraction analysis of compound **45a** has shown that hydrazone-thioamides of this type mainly exist in the *Z*-isomeric form.^{11b}



Scheme 35

Apart from other compounds of this series, hydrazones **45 b-d** (R²=H, R⁵=Ph, NR³R⁴=NHMe, NR¹R²=morpholin-4-yl (**b**); NR¹R²=NHC₆H₄Cl-4 (**c**); NR¹R²=NHC₆H₄Me-4 (**d**)) are a mixture of isomers that were separated by column chromatography. According to the NMR spectra, each isomer transforms to the original mixture in chloroform within 1h.

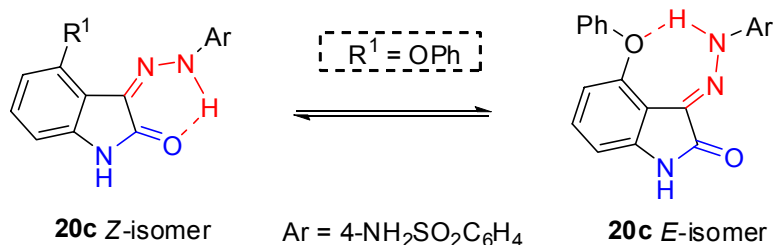
Hydrazones of isatine **20**, **36**, **49** (Schemes 5,12,18) and the corresponding thio derivatives **47**, **50** (Schemes 18), as viewed by their ¹H NMR spectra and data of X-ray analysis **47a** (R=Me),²¹ **20** (R¹=PhCO, R²=MeO, R³=C₆H₁₁ (**a**), R¹=PhCO, R²=H, R³=C₆H₁₁ (**b**))^{13a} exist predominantly in the *Z(cis)*-conformation, both in solution and in the solid state. This is due to the hydrogen bonding between the hydrazone NH and the carbonyl or thiocarbonyl group of indolinone (resp. thioindolinone)(Scheme 36).



Scheme 36

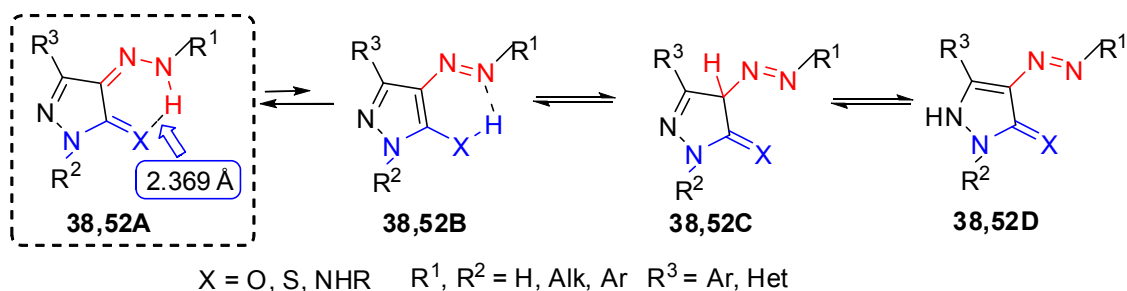
In the case of the presence of groups bearing heteroatoms with lone electron pair at position 4, an alternative hydrogen bond with the linker NH can be formed allowing the formation of the *E(trans)*-conformation.^{13a} ¹H NMR spectra of equilibrated samples **20c** (R¹=OPh) and **20d** (R¹=

CONH₂) correspond to a mixture of *Z*- and *E*-isomers. For example, the 4-phenoxy derivate **20c** was observed as 5 : 2 *Z* : *E* mixture after 10 days of equilibration (Scheme 37), and **20d** was found as 1 : 7 *Z* : *E* mixture.^{13a}



Scheme 37

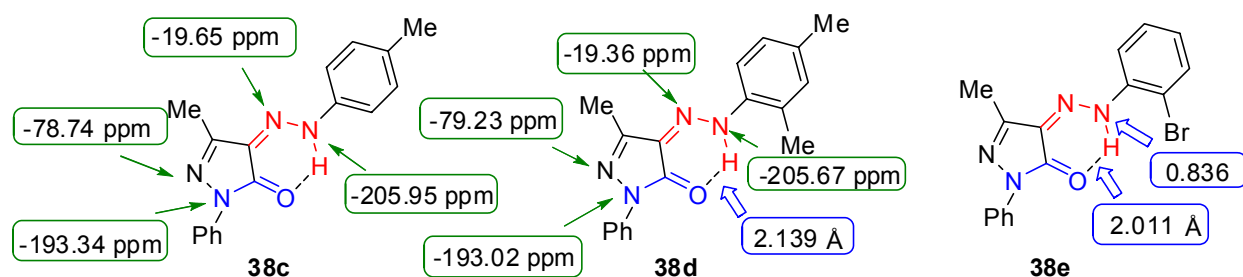
In principle, hydrazono-pyrazoles **38**(X=O) and **52**(X=S) (Schemes 13,19) can exist in four isomeric forms **A-D** (Scheme 38).^{22a,d,36} As shown by NMR spectroscopy in solution and X-ray structural determinations in the solid state, the tautomer **A** represents the energy preferred isomeric forms for most compounds **38,52**.



Scheme 38

To study the tautomerism of these compounds, 4-hydrazono-1*H*-pyrazol-5(4*H*)-ones **38** (X=O) labeled with ¹⁵N in the NHR¹ fragment were synthesized and their ¹H NMR spectra were carefully studied.^{22a} In chloroform solution at 38 and 60 °C, the unlabeled material **38 a,b** (X=O, R¹=R²=Ph, R³=Me (**a**), X=NHPh, R¹=R²=Ph, R³=Me (**b**)) gave a broad singlet at 13.5 ppm, whereas the compound labeled by ¹⁵N showed a doublet at 13.5 ppm, indicative of a proton attached to ¹⁵N. Since the value of the spin-spin coupling constant is quite large (*J* = 96 Hz), and since the area of the ¹⁵N proton peaks relative to the aromatic protons was in good ratio, these compounds must exist entirely in the hydrazono form under these conditions. The presence of one ¹⁵N-induced doublet in the ¹H NMR spectrum of **38a,b** indicates that only one geometric isomer of the hydrazono form exists in this solvent, while the far-downfield position of the NH peak suggests that the proton is involved in strong intramolecular hydrogen bonds.

^{15}N NMR experiments carried out by Connors *et al.*^{36b} (Scheme 39) and crystal structure determination support the formation of arylazopyrazolones as their hydrazone tautomers both in solution and the solid state.

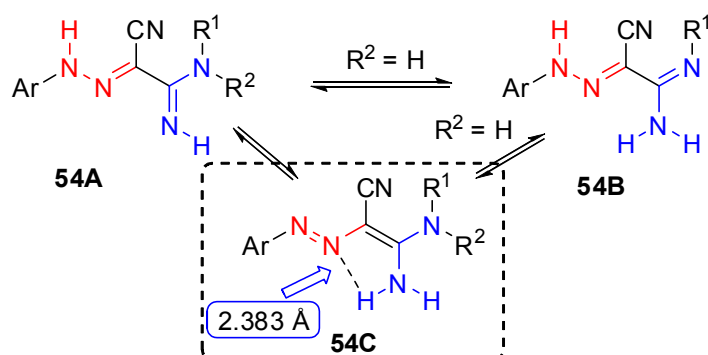


Scheme 39

For the imino derivatives **38** ($\text{X}=\text{NR}$) the equilibrium is shifted to the amino-azo form B.^{22d}

3.3 Hydrazono-amidines

In principle 2-arylhydrazonoacetamidines **54** can exist in three tautomeric forms A-C (Scheme 40).²⁷



Scheme 40

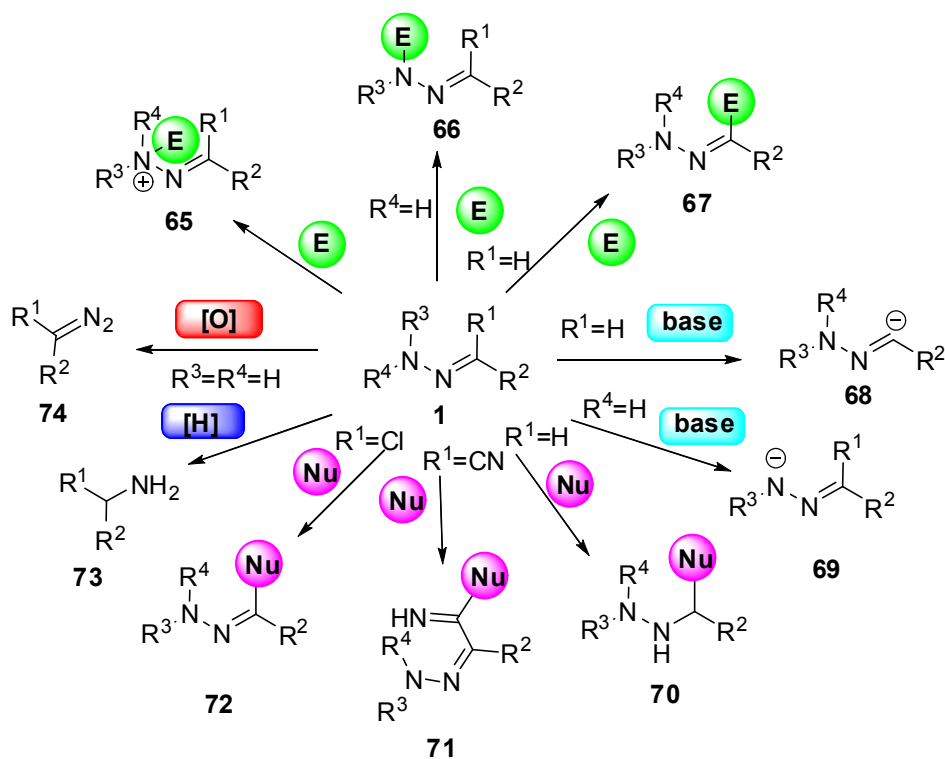
There are no NH proton signals in the ^1H NMR spectra of compounds **54** that would correspond to the hydrazono group. The signals of the amino groups of the amidine fragment are shown as a broad four proton singlet for compounds **54** ($\text{R}^1=\text{R}^2=\text{H}$) at 6.65 - 7.18 ppm; as a one proton singlet and a two proton singlet for compounds **54** ($\text{R}^1=\text{H}$, $\text{R}^2=\text{Me}$, Cy) at 7.15 - 7.42 ppm; and as a two proton singlet for compounds **54** ($\text{NR}^1\text{R}^2=\text{NAlk}_2$) at 6.58-6.97 ppm. IR spectra of compounds **54** show a few broad bands between 3200-3450 cm^{-1} confirming the presence of amino groups. X-Ray diffraction analysis of single crystal for **54** ($\text{NR}^1\text{R}^2=\text{piperidin-1-yl}$, $\text{Ar}=4\text{-MeOC}_6\text{H}_4$) show the existence of compounds **54** in the *E,E*-arylazo tautomeric form **C** with planarity of double bonds $\text{C}=\text{C}$ and $\text{N}=\text{N}$ bonds. It is worth noting the presence of the

hydrogen bond of the amidine hydrogen with the nitrogen atom of the azo group as shown in Scheme 40.

Indeed, of hydrazoneamide, -thioamide and -amidine molecules contain hydrogen bonds that take part in stabilization of various isomeric forms. In contrast to hydrazoneamides and -thioamides that exist in the hydrazone form, hydrazoneamidines exist preferably in the arylazo tautomeric form both in solution and in the solid state.

4. Chemical properties of hydrazone-amides, -thioamides and -amidines

Hydrazones exhibit a varied reactivity, taking part in reactions with nucleophiles, electrophiles and other chemical reagents. Being ambident nucleophiles, hydrazones react with electrophilic reagents with participation of either the nitrogen atom (compounds **65,66**),^{3a,10} or the carbon atom of the azomethine group (compounds **67**).^{3a,10} Strong bases deprotonate hydrazones to form anions of types **68,69**, whereas nucleophiles attack the azomethine carbon atom to form products of both addition **70,71** and substitution **72**.^{3,6} Furthermore, hydrazones can be reduced to amines **73** or oxidized to diazo compounds **74**³ (Scheme 41).



Scheme 41. Reactions of hydrazones with different type of reagents.

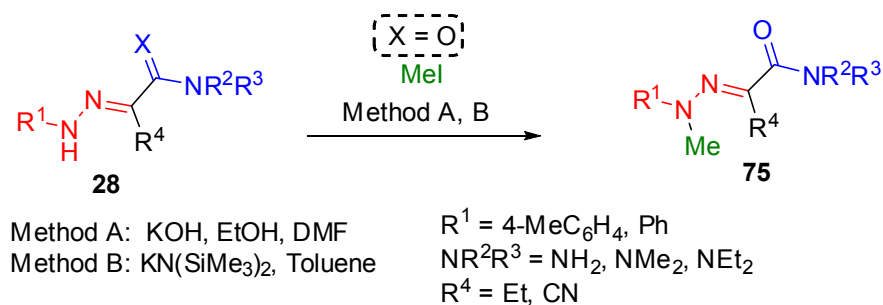
4.1 Reactions with nucleophiles

Hydrazone of aldehydes and ketones are prone to form the addition products to the C=N bond, rather than to form the products of substitution. In contrast, in the case of the presence of good leaving groups at the carbon atom, the substitution reactions occur smoothly to give compounds with new substituents.⁶ The nucleophilic reagents that can be used in these reactions are alkali hydroxides, alkoxides, azides, ammonia, amines and hydrazines. Thus, substitution reaction of halogen by amines is used to prepare amidrazones **60** (Scheme 22).

The introduction of amide and thioamide groups to the molecules of hydrazones drastically expands the scope of these reactions. Most of such reactions are used to prepare new derivatives of hydrazones bearing amide, thioamide and amidine groups. Thus, 2-hydrazonoacetamides **11**, isatine hydrazones **36**, **49**, and hydrazonopyrazolones **38** react with Lawesson's reagent to form the substitution products of the oxygen atom by sulfur, namely the thioamides **45-47**, **50**, **52** (Scheme 17-19). The cyano group of hydrazonomalononitriles **41** is capable of adding hydrogen sulfide to give 2-hydrazonothioacetamide **44** (Scheme 16). Primary and secondary amines can also react with hydrazonomalononitriles **41** to form hydrazono-amidines **54** (Scheme 20).

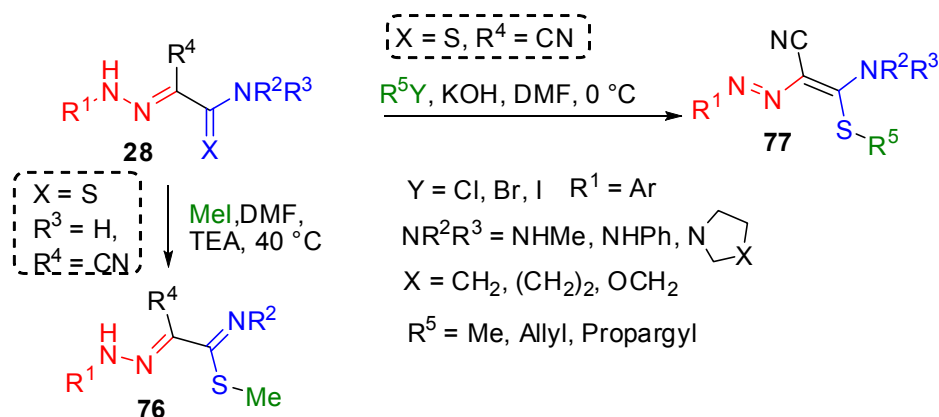
4.2 Reactions with electrophiles

The introducing of amide, thioamide and amidine groups to molecules of hydrazones of aldehydes and ketones gives new centers that are capable of reacting with electropilic reagents. Alternative reactions can take place to give products of substitution at both hydrazono and new groups. Alkylation of arylhydrazones **28** (X=O) is directed to NH of hydrazono group to afford disubstituted hydrazones **75**. This reaction can be recommended as the methods of choice to prepare disubstituted hydrazones of type **75** (Scheme 45).^{16l,t,37}



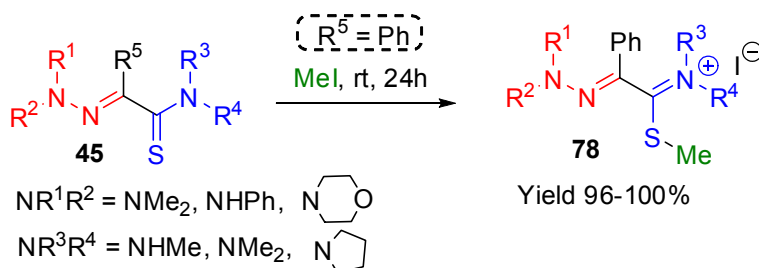
Scheme 42

The sulfur atom of 2-arylhydrazonothioacetamides **28** (X=S) takes part in reaction with alkyl halides to form thioimidates **76** or thioaminals **77** (Scheme 43).^{17b,27}



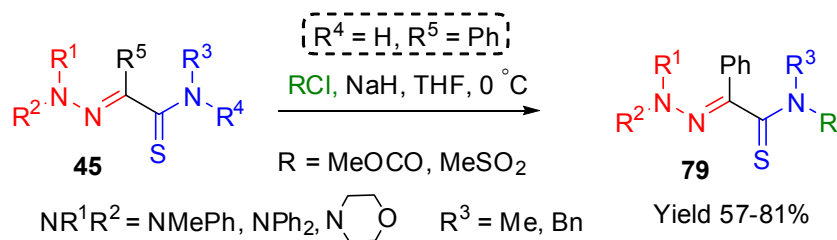
Scheme 43

In contrast to 2-cyano hydrazones **28**, 2-phenylhydrazones **45** can slowly react with alkyl iodide in the absence of a base to form thioimminium salts **78** (Scheme 44).^{11a}



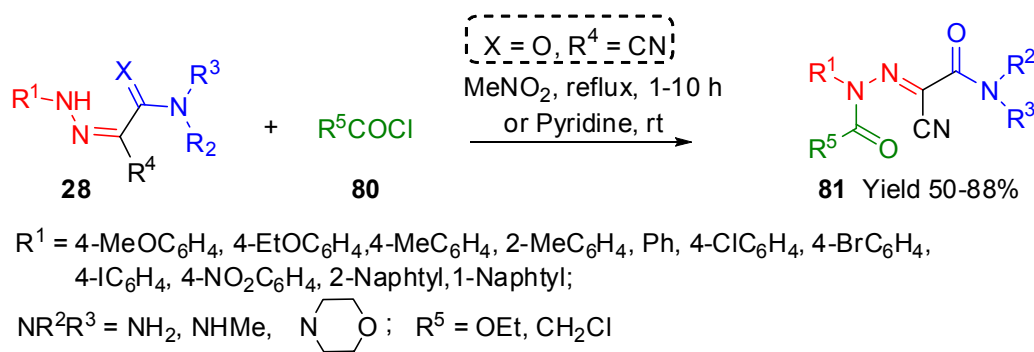
Scheme 44

Reactions of 2-alkylhydrazono-2-phenylethanethioamides **45** with less polarizable electrophiles take place at the nitrogen atom of the thioamide function to give N-acyl (or –sulfonyl) thioamides **79**.^{11c}



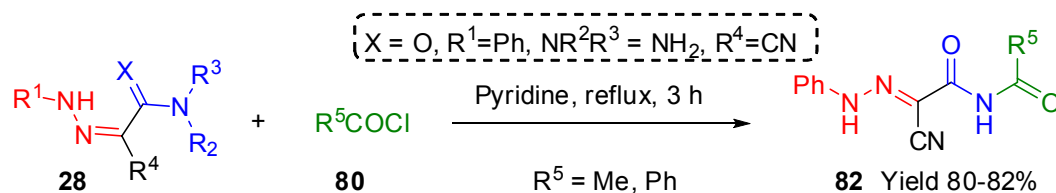
Scheme 45

Arylhydrazonoacetamides **28** react with chloroacetic acid and ethyl chloroformate to give corresponding acylated hydrazones **81**^{16b,f,38} (Scheme 46).



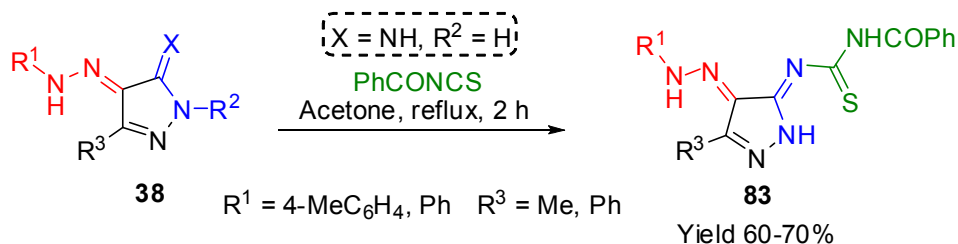
Scheme 46

Reactions of 2-phenylhydrazonoacetamide **28** with acetyl chloride and benzoyl chloride are directed to the amide group to form N-acylamide **82** (Scheme 47).¹⁶¹



Scheme 47

Arylhydrazono-1*H*-pyrazol-5(4*H*)-imines **38** ($X = NH$) react with benzoyl isothiocyanate to form 4-(2-arylhydrazono)-1*H*-pyrazol-5(4*H*)-ylidene)carbamothioyl)benzamide **83**.^{39,29h}

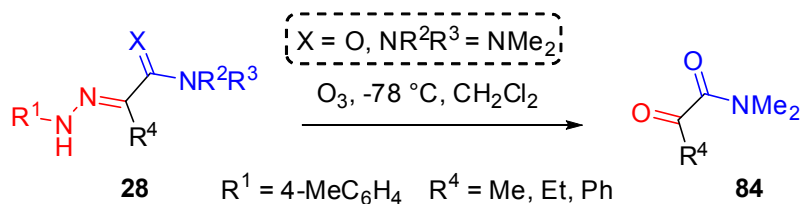


Scheme 48

Indeed, the examples of the study of alkylation and acylation reactions of hydrazono-amides and thioamides are sometimes contradictory and not numerous enough to make conclusions on the general reactivity of these compounds in reactions of electrophilic substitution. They are not studied at all for hydrazono-amidines. More information on the matter can be found in part 4.4.

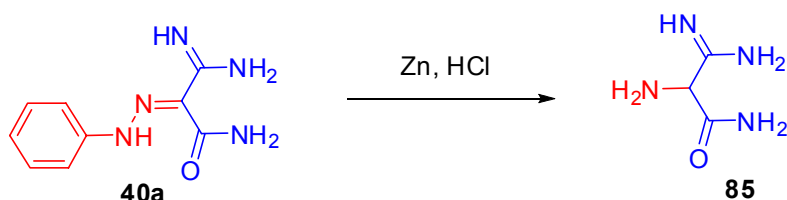
4.3 Oxidation and reduction

Oxidative substitution of hydrazono group by oxygen occurs when hydrazones **28** ($X=O$) were reacted with ozone at low temperature to form 1,2-dicarbonyl compounds **84** (Scheme 49).^{16t}



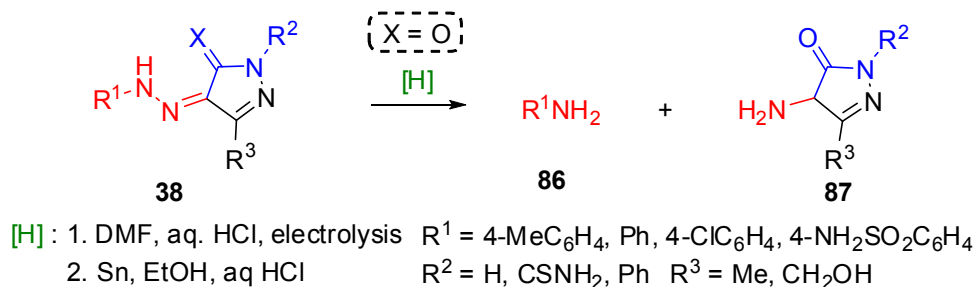
Scheme 49

Reduction of 2-phenylhydrazonoacetamidine **40a** with zinc dust in acidic medium led to the cleavage of the hydrazono N-N bond to form 2,3-diamino-3-iminopropanamide **85** in good yield (Scheme 50).^{23a,b,e}



Scheme 50

In somewhat similar manner, both polarographic reduction and reduction with tin of 4-(2-arylhydrazono)-1*H*-pyrazol-5(4*H*)-ones **38** ($X=O$) may take place, cleaving the hydrazono group to afford 4-amino-1*H*-pyrazol-5(4*H*)-ones **87** (Scheme 51).⁴⁰



Scheme 51

4.4 Use of hydrazone-amides, -thioamides and -amidines in the synthesis of heterocyclic compounds

The hydrazono-amide, -thioamide and -amidine molecules contain a number of nucleophilic and electrophilic centers. Therefore, one can envisage that these compounds will react with bifunctional chemical reagents to form cyclic systems. Depending on the nature of the reagents, and the reactivity of the nucleophilic and electrophilic centers of the hydrazones, different interactive combinations can be realized to afford a large variety of heterocyclic compounds (Figure 3).

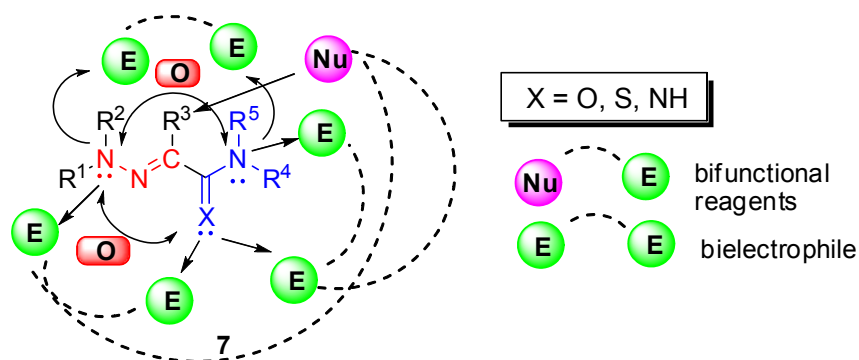
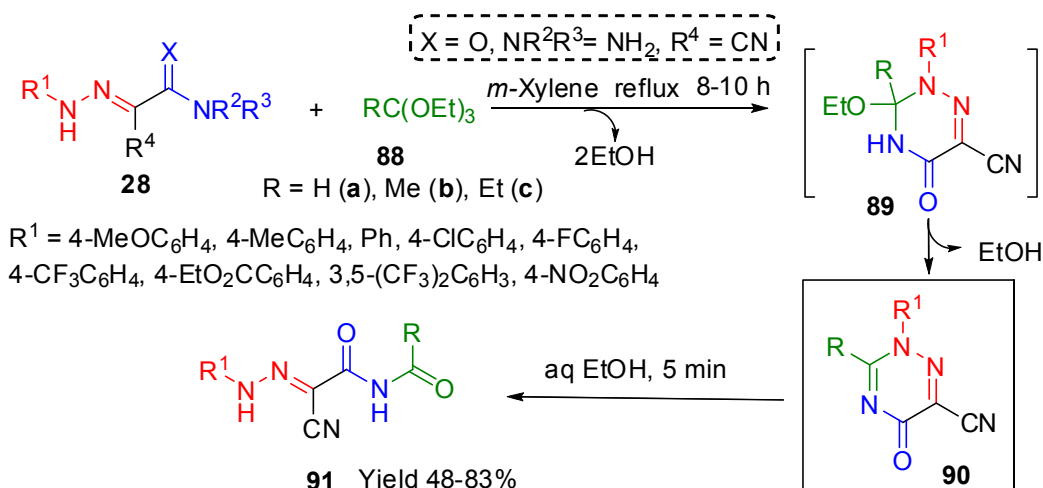


Figure 3. The variety of options leading to heterocyclic compounds.

Heterocyclization reactions of compounds **7** are the result of the reactions (i) with bifunctional reagents bearing two electrophilic groups, (ii) with bifunctional reagents having one electrophilic and one nucleophilic group; (iii) by cycloaddition reactions; (iv) intramolecular condensation and (v) reactions with oxidation reagents.

4.4.1 Reactions with derivatives of formic acid, ketones, carbon disulfide and thiophosgene.

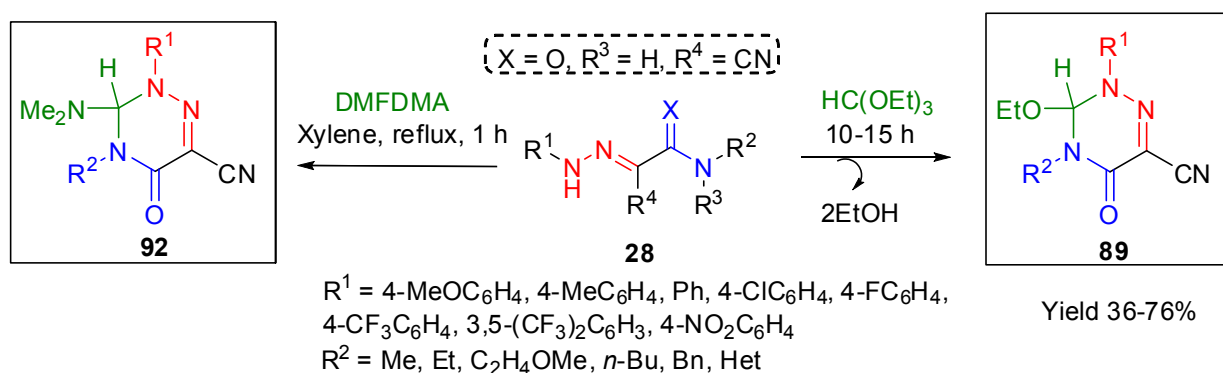
This part summarizes the literature on the reactions of bielectrophilic reagents providing one atom (carbon) to the newly formed heterocycle. Reactions of arylhydrazonoacetamides **28** (X=O, NR²R³=NH₂) with orthoesters **88** were shown to afford 1,2,4-triazinones **90** in high to moderate yields. A systematic study of the reaction conditions with variation of the solvent, temperature and catalyst led to a method of choice involving the use of dry boiling *meta*-xylene while azeotropically removing the ethanol formed (Scheme 52).^{16q-s}



Scheme 52

The reaction mechanism involves the formation of a double and a single C-N bond accompanied by the elimination of three molecules of ethanol. 2,5-Dihydro-1,2,4-triazines **90** are not stable in the presence of water and transform to acyl amides **91** presumably by addition of a molecule of water to the C=N bond of the 1,2,4-triazine ring, followed by cleavage of the C-N bond and formation of an acyl group. This process is accelerated by addition of acids.

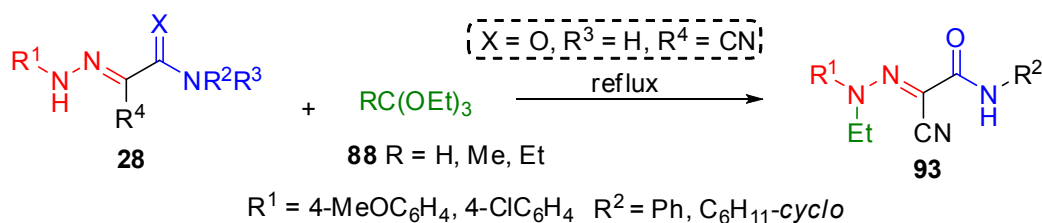
Reaction of hydrazones **28** ($X=O, R^2=\text{Alk}, \text{Het}, R^3=\text{H}$) with triethyl orthoformate or dimethylformamide dimethylacetal (DMFDMA) under reflux leads to the formation of isolable 2,3,4,5-tetrahydro-1,2,4-triazines **89** and **92** respectively (Scheme 53).^{16q-s,u}



Scheme 53

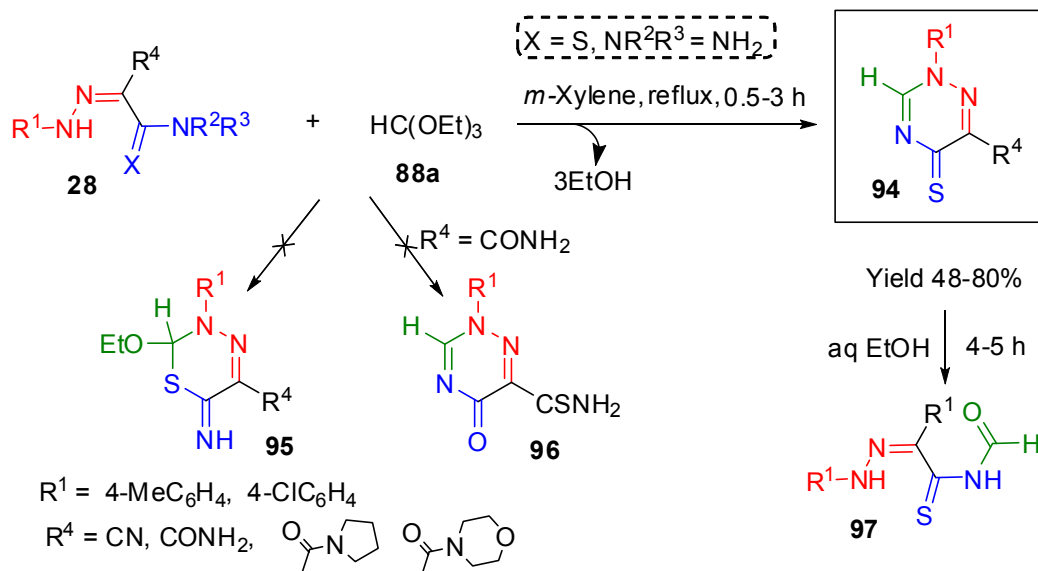
The formation of the product **89** ($R^2=\text{Alk}$) confirms that the reaction mechanism of hydrazono-amides **28** ($X=O, NR^2R^3=NH_2, R^4=CN$) with orthoethers takes place *via* triazines **89** ($R^2=H$) (Scheme 52). Tetrahydrotriazinones **89** ($R^2=\text{Alk}$) are crystalline substances which are quite stable to acids and bases at room temperature but when boiled in ethanol with an equimolar amount of sulfuric acid they decompose to the starting hydrazones **28** ($X=O$).

In contrast to the reaction of derivatives **28** ($X=O$, $NR^2R^3=NH_2$, $R^4=CN$) with orthoesters **88** (Scheme 52), the reactions of compounds **28** ($X=O$, $NR^2R^3=NHAlk$, $R^4=CN$) with triethyl orthoacetate **88b** and orthopropionate **88c** and the reaction of hydrazones **28** ($X=O$, $NR^2R^3=NHPh$, $NHCy$) with all types of orthoesters **88** leads to N-ethylhydrazones **93** (Scheme 54). Their formation was explained by the decrease in reactivity of the amide NH group of hydrazone **28** ($X=O$, $NR^2R^3=NHCy$, $NHPh$, $R^4=CN$) by introducing of a bulkier aryl or cyclohexyl substituent that hinder cyclization of the intermediates.^{16s} Migration of the ethyl group to the N-atom of the hydrazone fragment and elimination of ethyl formate then occurs.



Scheme 54

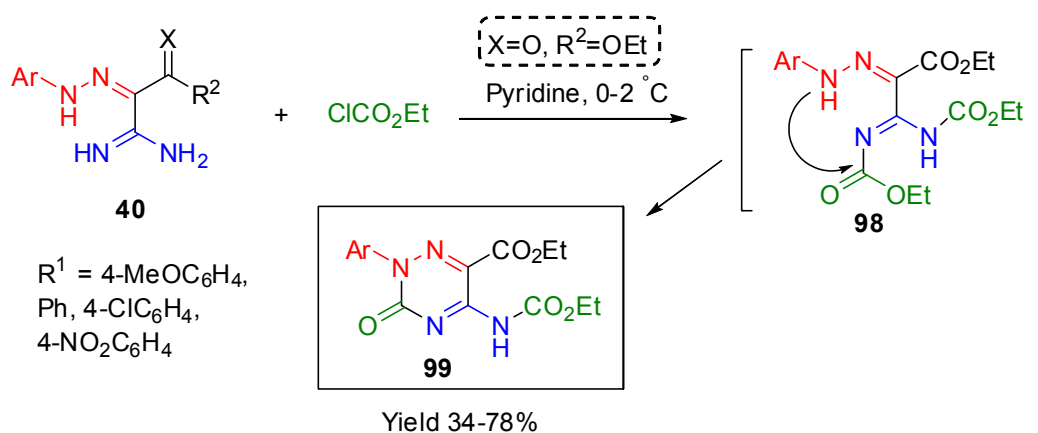
Reactions of 2-arylhydrazonothioacetamides **28** ($X=S$) with ethyl orthoformate **88a**, irrespective of the substituents, take place with participation of the nitrogen atoms of both the thioamide and hydrazono group to afford 1-aryl-1,4-dihydro-1,2,4-triazine-4-thiones **94** rather than thiazines **95** or triazine-4-ones **96** (Scheme 55).^{17b} The observed selective formation of product **96** in the reaction of thioamide **28** ($X=S$, $NR^2R^3=NH_2$, $R^4=CONH_2$) is indicative of the higher reactivity of the thioamide nitrogen in comparison to its sulfur atom; and also shows that the hydrazono NH group is more reactive than the carboxamide NH.



Scheme 55

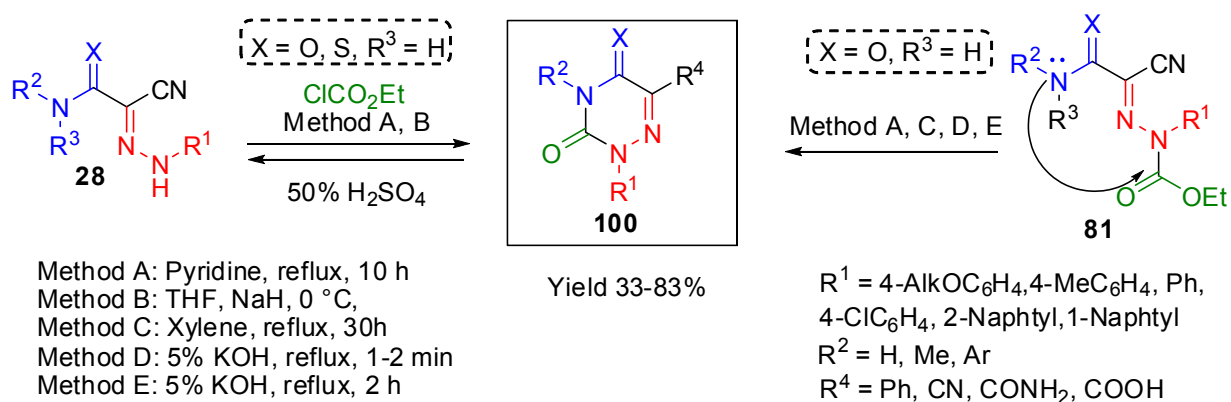
5-Thioxo-2,5-dihydro-[1,2,4]triazines **94** similar to the corresponding 5-oxo-[1,2,4]triazines **90** are capable of transforming to formylthioamides **97** after heating at reflux in organic solvents in the presence trace of water. It is worth noting that compounds **94** are slightly more stable than their oxygen analogs **90**.

The amidinohydrazones **40** ($X=NH$, $R=NH_2$) react with two moles of ethyl chloroformate to give ethyl 2,3-dihydro-5-ethoxycarbonylamino-1,2,4-triazine-6-carboxylates **99** (Scheme 56).^{23d}



Scheme 56

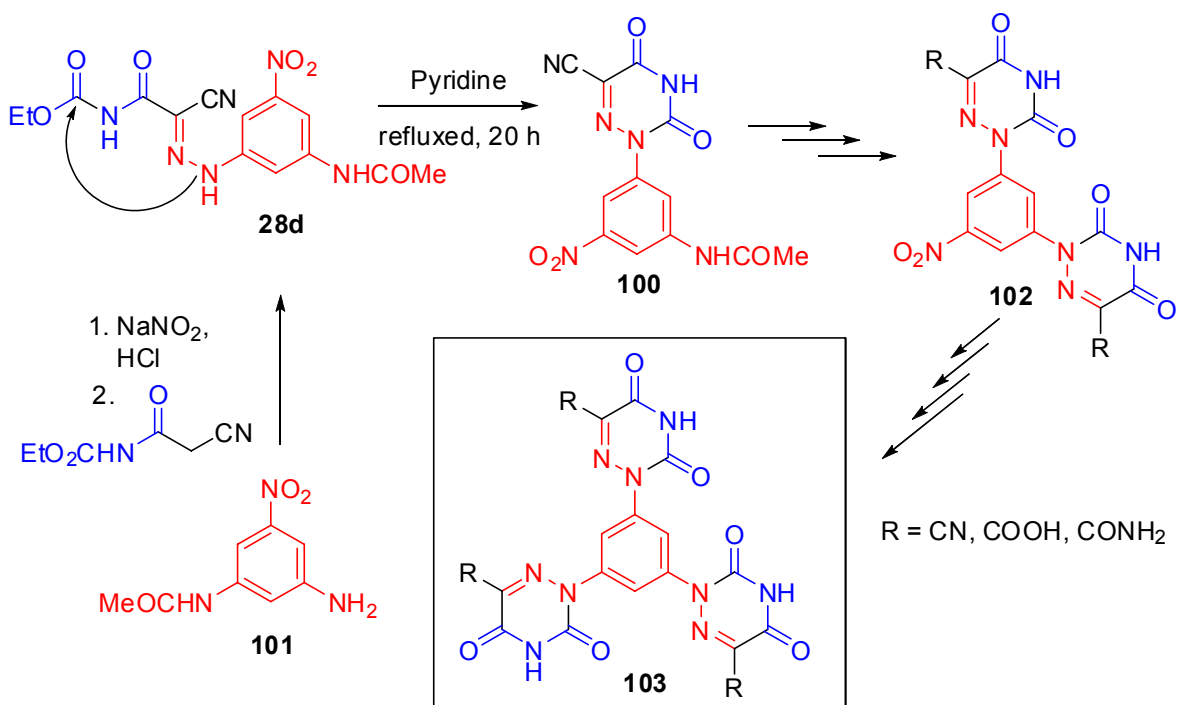
Arylhydrazonoacetamides **28** cyclize on heating with ethyl chloroformate in anhydrous pyridine solution to give the corresponding 1-aryl-5-cyano-6-azauracils **100**.^{11d,16a-f,23d,38} Intermediates in this reaction are the product of acylation of the hydrazone group, N-carbethoxyhydrazones **81**. Their intramolecular cyclization leads to the same 1,2,4-triazin-3,5-dione **100** (Scheme 57).



Scheme 57

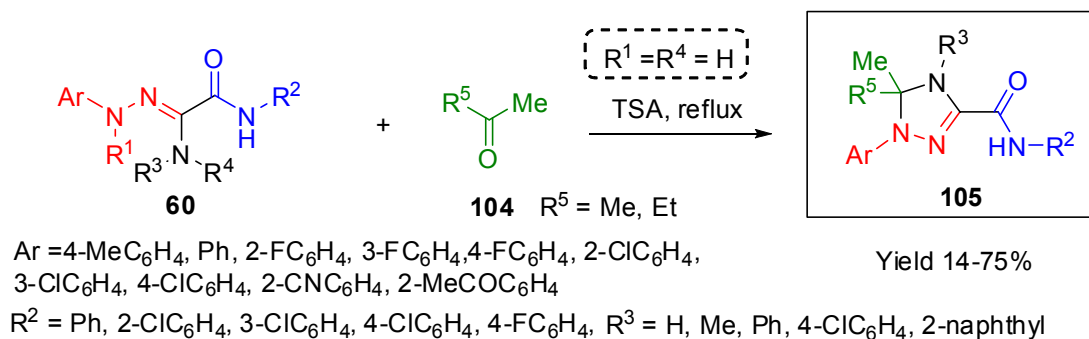
Arylhydrazones **28** with an ethoxycarbonyl group attached to the nitrogen atom of the carbamoyl group undergo similar cyclization to 1,2,4-triazines **100**.^{16a-f} Depending on the

conditions of the process depicted in Scheme 57, 2,3,4,5-tetrahydro-[1,2,4]triazines **100** were prepared containing cyano-, carboxamide or carboxy groups at position 6 of the ring.^{16a} Based on this reaction the authors^{16c} have prepared 1,3-bis(6-azauracil-1-yl)benzenes **102** and 1,3,5-tris(6-azauracil-1-yl)benzenes **103** from 3-amino-5-nitroacetanilide **101** via several intermediates (Scheme 58).



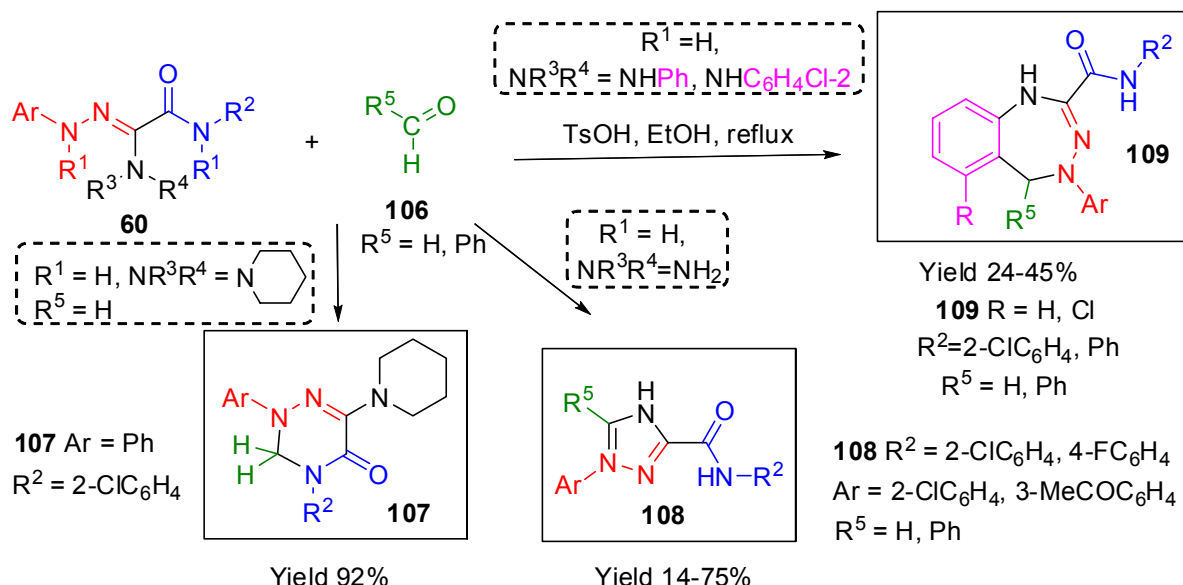
Scheme 58

Reaction of amidrazones **60** with alkyl ketones **104** under acidic catalysis includes attack of the latter at the NH functions of the hydrazono and amino groups of compounds **60** to afford 4,5-dihydro-1*H*-1,2,4-triazoles **105** (Scheme 59).^{28b,d}



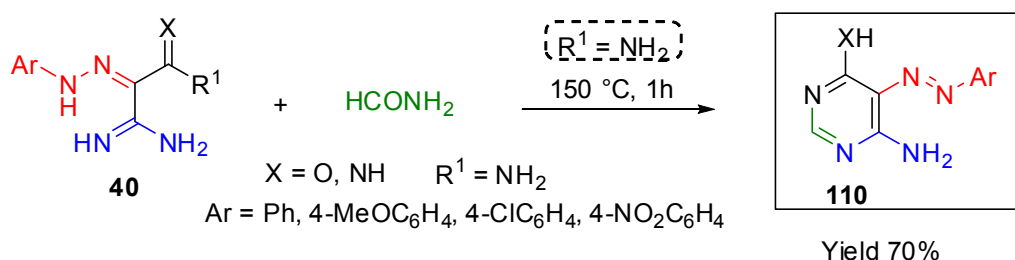
Scheme 59

Reaction of amidrazones **60** with aldehydes **106**, depending of the nature of the hydrazono, 2-amino and amide groups led to formation of five-, six- and seven-membered heterocyclic compounds: 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones **107**, 1-aryl-1*H*-1,2,4-triazole-3-carboxanilide **108**, or benzo- dihydrotriazepines **109**, respectively (Scheme 60).^{28b,d}



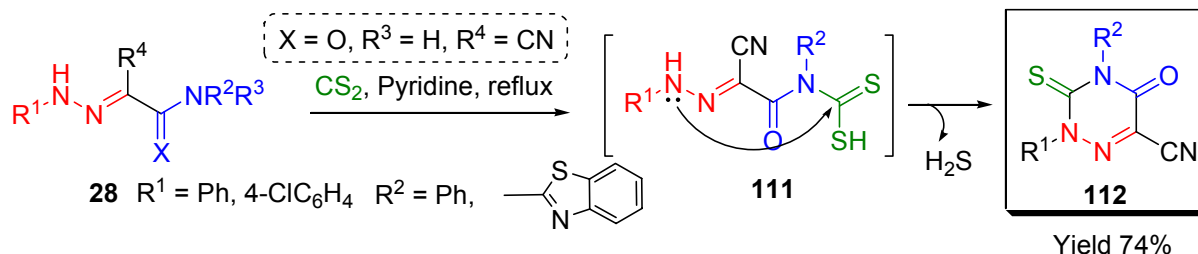
Scheme 60

Reaction of hydrazones of type **40** with formamide takes place with participation of the amidine and C(X)NH₂ groups to give 5-phenylazopyrimidine **110**. It is worth noting that the hydrazono group of compounds **40** does not take part in the cyclization process (Scheme 61).^{23c}



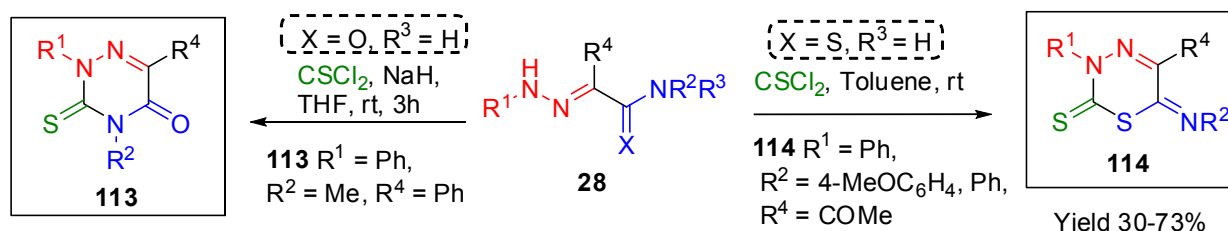
Scheme 61

Cyclocondensation of arylhydrazonoacetamides **28** ($X=O$) with carbon disulfide in pyridine at reflux temperature furnished the 1,2,4-triazinone derivative **112** in good yield. The formation of compound **112** is assumed to proceed *via* initial attack of the secondary amino group of hydrazone **28** ($X=O$) to the thiocarbonyl group of the carbon disulfide followed by intramolecular cyclisation accompanied by elimination of hydrogen sulfide (Scheme 62).^{16u,41}



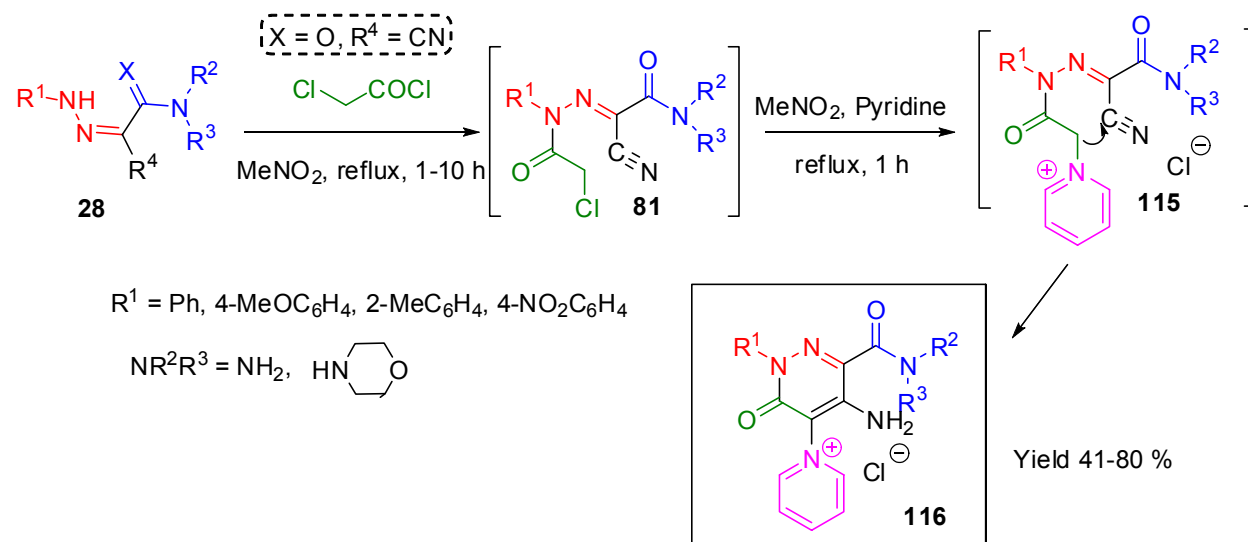
Scheme 62

2-Arylhazonoacetamides **28** can react with thiophosgene, similarly to the reaction with carbon disulfide, to give 3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one **113**.^{11d} Thioacetamides **28** ($\text{X}=\text{S}$) react with thiophosgene by an alternative way, involving the thioamide sulfur atom and the NH fragment to form 3,6-dihydro-2H-1,3,4-thiadiazine-2-thiones **114**.^{17h}



Scheme 63

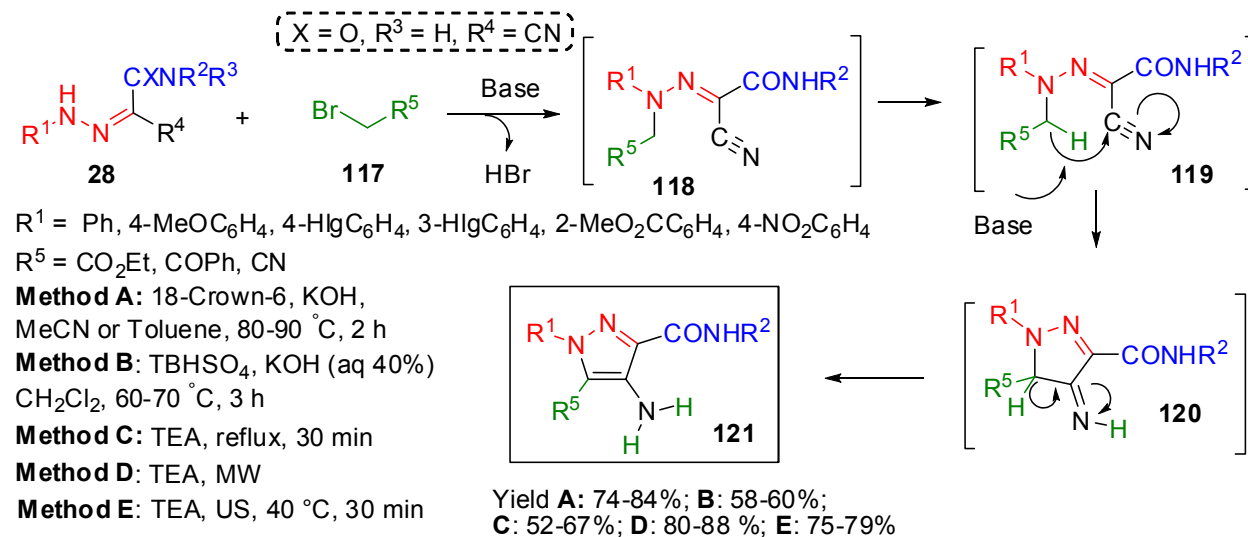
4.4.2 Reactions with α -halocarbonyl compounds. α -Halocarbonyl compounds, such as α -chloroacetic acid derivatives and ketones bearing in α -position halo atoms can react as both alkylating and acylating reagents and therefore are widely used in organic syntheses to prepare various heterocyclic compounds. Reactions of hydrazones with halocarbonyl compounds have been used in the synthesis of compounds bearing both cyano and active methylene groups, capable of participating in Thorpe-Ziegler cyclization to form various five- and six-membered heterocyclic compounds.^{16o,v,w,17b-e,38b,42} Arylhazonoacetamides **28** ($\text{X}=\text{O}$) react with chloroacetic acid chloride to give N-chloroacetyl derivatives **81**.^{38b} Subsequent reaction with pyridines generates hydrazonoacetoneitriles that undergo Thorpe-Ziegler cyclization, affording 1-(4-amino-6-oxo-pyridazin-5-yl)pyridinium chlorides **116** (Scheme 64). Based on these data we assume another structure for intermediate product in reaction of hydrazone **28** with carbon disulfide (Scheme 62).



Scheme 64

It is worth noting that the reaction of hydrazones **28** ($\text{X}=\text{O}$) with chloroacetyl chloride occurs on the nitrogen atom of the hydrazono group, similarly to the reaction with other acylating reagents.

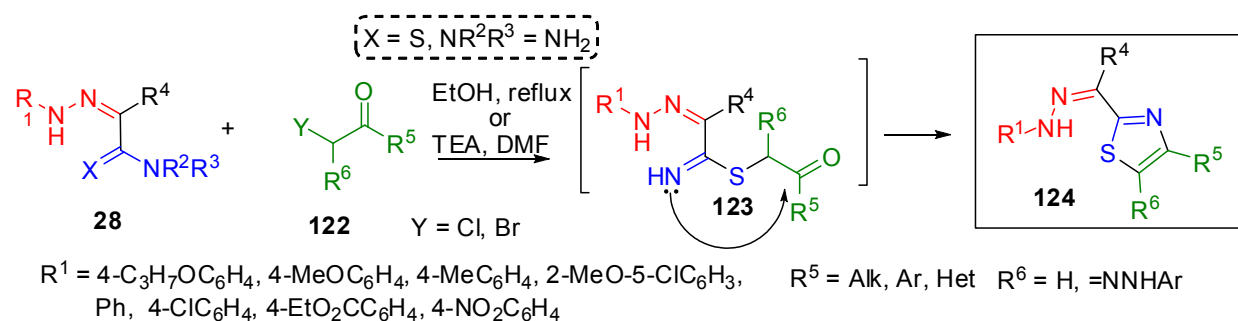
Thorpe-Ziegler cyclization of α -arylhydrazono cyanacetamide **28** ($\text{X}=\text{O}$) with α -bromo ketones, esters or nitriles **117** in different type base catalyst including phase transfer conditions (TBHSO_4 - tetrabutylammonium hydrogen sulfate) resulted in 4-amino-1-aryl-3,5-disubstituted-1H-pyrazoles **121** which represent an important building block for the construction of the fused heterocycles (Scheme 65).^{160,v,w}



Scheme 65

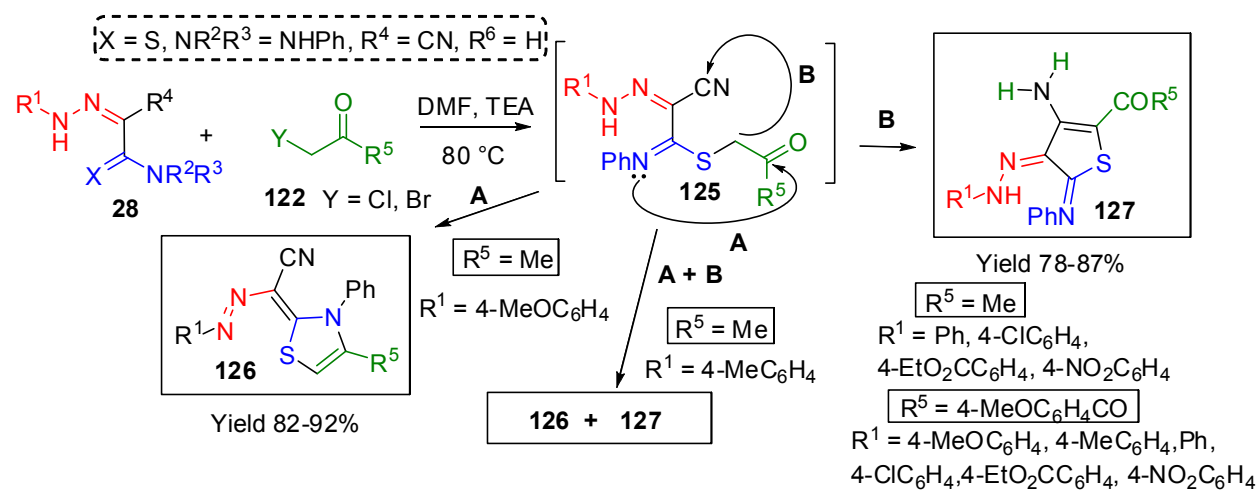
A plausible mechanism for the Thorpe reaction is proposed in Scheme 65. The initial HBr removal from α -bromo ketone or ester and α -arylhydrazononitriles **28** ($X=O$) resulting in intermediate **118** followed by the intramolecular nucleophilic addition of CH onto the nitrile group, gave imines **120** that could tautomerize to the aromatic enamines (4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **121**). The yield of the reaction increased under microwave (Method D) and ultrasound (Method C) irradiation.^{16w}

In contrast to **28** ($X=O$) the alkylation of unsubstituted thioamides **28** ($X=S$, $NR^2R^3=NH_2$) with bielelectrophiles **122** is directed to the sulfur atom, generating thioimidates **123**. Subsequent cyclization of the latter leads to thiazoles **124** (Scheme 66).^{17b-e,42}



Scheme 66

However, the introduction of a phenyl group at the nitrogen atom of the thiocarbamoyl radical leads to the formation of thiazol-2(3*H*)-ylidenes **126** and 4,5-dihydrothiophenes **127** or their mixture *via* both Hantzsch (A) and Thorpe-Ziegler (B) pathways, respectively (Scheme 67).^{17c,d}

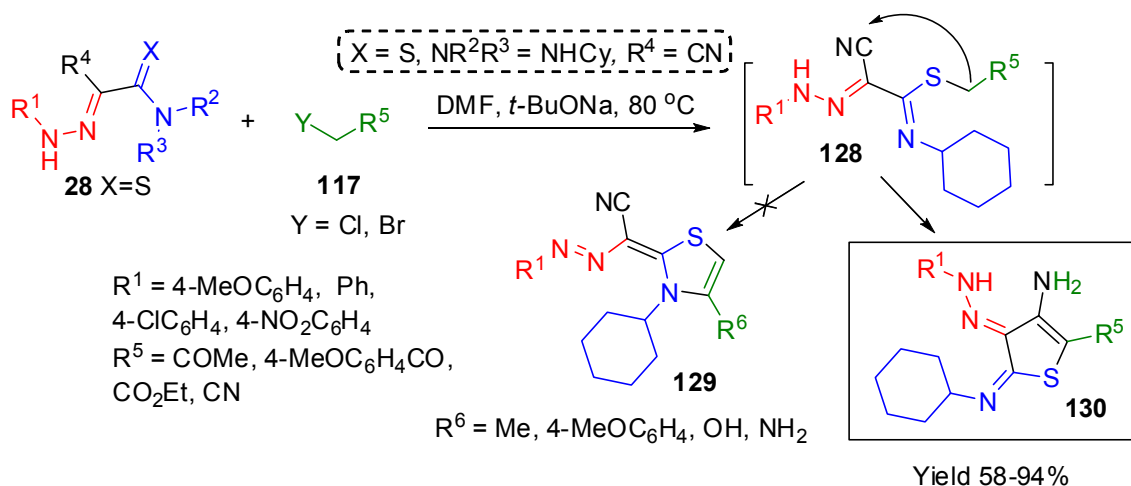


Scheme 67

The formation of the thiophene ring in the reaction of N-phenylthioacetamides **28** (X=S, NR²R³=NHPh) with halo ketones **122** (R⁶=H) can be explained by the decrease of the nucleophilicity of the thioamide nitrogen atom and the higher acidity of the SCH₂ group of compounds with electron-withdrawing substituents that enhance the Thorpe-Ziegler reaction leading to thiophenes **127**.

The arylhydrazone group does not participate directly in the reaction, but affects the direction of the cyclization since it is a “transmitter” of the electronic effects from rather distant parts of the molecule to the reaction site.

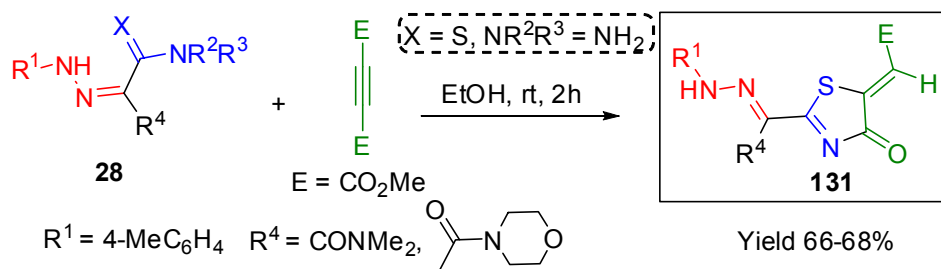
The reaction of arylhydrazonocyanothioacetamides **28** (X=S, NR¹R²=Cy) containing an N-cyclohexyl fragment with chloroacetone, phenacyl bromide, ethyl chloroacetate, and chloroacetonitrile was studied and it was shown that such a substituent with a large steric effect in the thioamide group alters the direction of intramolecular cyclization of the thioimide intermediate (Scheme 68).^{17f,g} Rather than the expected Hantzsch reaction, which usually leads to the formation of thiazol-2(3*H*)-ylidenes **129** under these conditions, the only products were 3-amino-4-arylhazono-4,5-dihydrothiophenes **130**.



Scheme 68

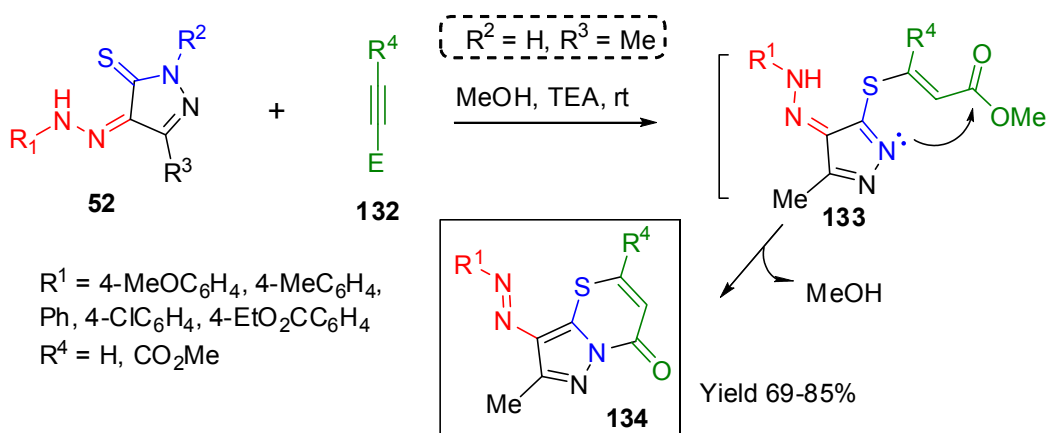
4.4.3 Reactions with of acetylene carboxylic esters. Reactions of acetylenecarboxylic esters with compounds with a number of nucleophilic centers are of interest to organic chemists as convenient methods for the synthesis of various heterocyclic compounds.⁴³ Various directions for this reaction can take place, resulting in the formation of regio- and stereoisomers.

Despite of the presence of five nucleophilic centers, hydrazonothioacetamides **28** (R¹ = NR₂) react with DMAD to afford thiazolidines **131** selectively (Scheme 69).^{17j}



Scheme 69

The formation of a six-membered ring occurs in the reaction of 4-aryldiazonopyrazole-5-thiones **52** with acetylene carboxylic esters **132** in methanol in the presence of triethylamine to afford thiazino-pyrazoles **134** as exclusive products. The hydrazono group does not take part in the formation of the bonds of the new ring, but enhances the formation of the final product, providing a hydrogen atom to the nitrogen-2 atom of the first ring (Scheme 70).^{22c}

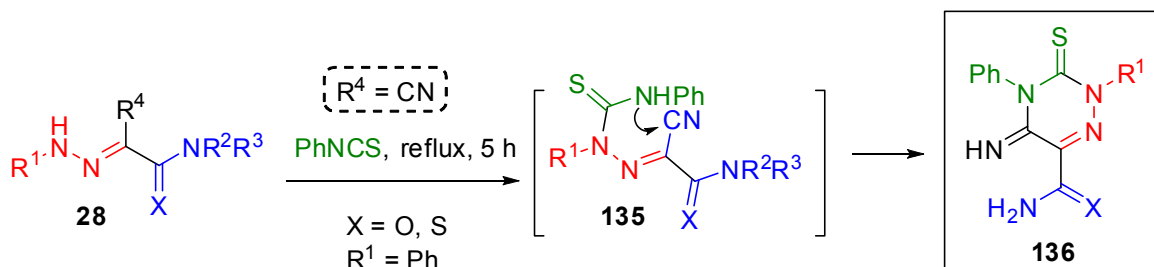


Scheme 70

The reactions shown in the schemes 69 and 70 prove that the diene systems ($\text{C}=\text{N} + \text{C}=\text{S}$ bonds) of compounds **28** ($\text{X}=\text{S}$) and **52** are not reactive, although the close structural analogs of **28**, 2-cyanothioacrylamides readily react with DMAD, methyl propiolate, and N-phenyl maleimides *via* a 4+2 cycloaddition pathway to give thiopyrans, irrespective of the electronic or spatial effects of the substituents in the thioamide group and in position 3 of the 1-thiabuta-1,3-diene system.⁴⁴

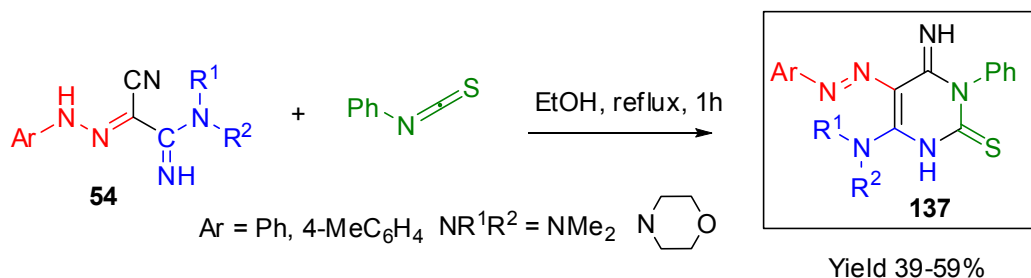
4.4.4 Reactions with reagents containing both electrophilic and nucleophilic functions. Hydrazones can react with isothiocyanates to form compounds with a thiocarbamoyl group. In the case of presence of the cyano group at position 2 of the hydrazone, the highly electrophilic carbon atom of the intermediate thiosemicarbazone **135** undergoes cyclisation to 4,5-dihydro-

1,2,4-triazine-3(2*H*)-thiones **136**.⁴⁵ Indeed, both nucleophilic and electrophilic centers of hydrazones **28** take part in the process of heterocyclization (Scheme 71).



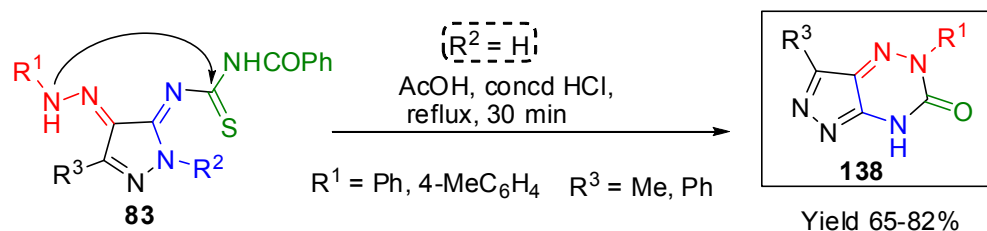
Scheme 71

Reaction of hydrazono-amidine **54** with phenylisothiocyanate begins with the attack of the latter to the NH of the amidine group, followed by the reaction of the cyano group with the thiocarbamoyl fragment to form 5-arylaazo-4-imino-1,4-dihydropyrimidin-2-thiones **137**. The hydrazono group does not take part in the reaction, other than of providing a hydrogen atom to the new ring (Scheme 72).²⁴



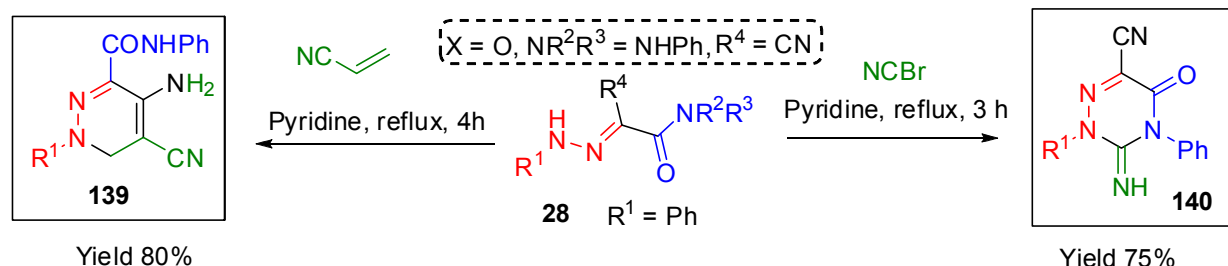
Scheme 72

Another type of heterocyclization occurs when pyrazol-5-yl-thioureas **83** (Scheme 48) were boiled in a mixture of acetic and hydrochloric acids to form 2,4-dihydro-pyrazolo[3,4-*e*][1,2,4]triazin-3-ones **138** (Scheme 73).³⁹



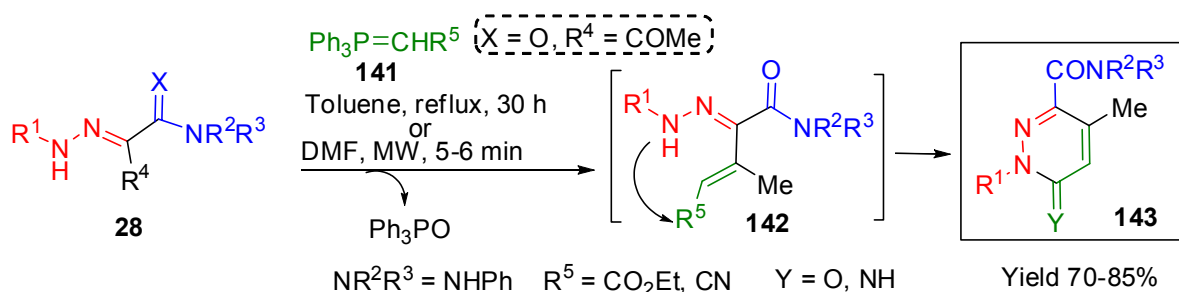
Scheme 73

2-Cyano-2-phenylhydrazonoacetamide **28** ($X=O$) reacts with acrylonitrile in boiling pyridine to afford 2,3-dihydropyridazine **139**, while its reaction with cyanogen bromide leads to 3-imino-3,4-dihydro-1,2,4-triazin-5(2*H*)-one **140** (Scheme 74).⁴¹



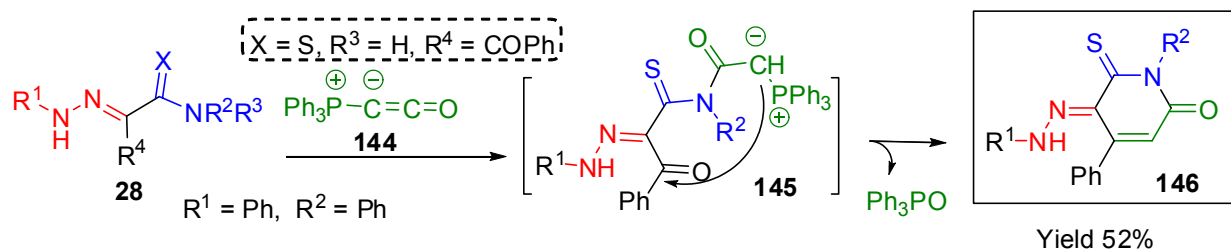
Scheme 74

Condensation of Wittig reagents **141** with arylhydrazonoacetamide **28** ($X=O$) by conventional and by microwave heating techniques furnished the corresponding pyridazinones and iminopyridazines **143** (Scheme 75).⁴⁶



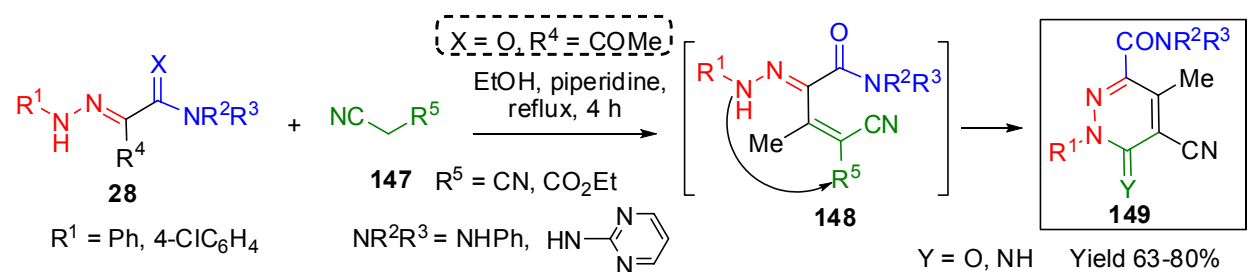
Scheme 75

The reaction of more active phosphacumulen-ylide **144** with 2-hydrazonothioacetamide **28** ($X=S$) takes place by another way to form pyridine-thione **146** via intermediate **145** as depicted in the Scheme 76. The ring formation is the result of bridging of thioamide and ketone groups by ylide **144**. It is worth noting that the nitrogen atoms of the hydrazono group do not take part in the heterocyclization.⁴⁷



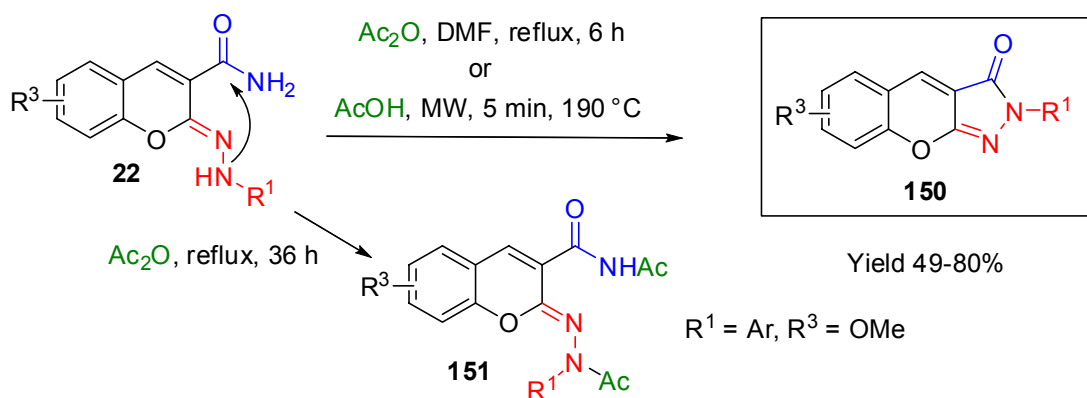
Scheme 76

Active methylene compounds such as malononitrile and ethyl cyanoacetate **147** react with 2-acetyl-2-hydrazonoacetamide **28** ($X=O$) in ethanol in the presence of a catalytic amount of piperidine to generate a hydrazone of type **148**.⁴⁸ The latter, *via* interaction of the hydrazono group with cyano- or ester functions, affords 6-imino- and 6-oxo-pyridazines **149**, respectively (Scheme 77).



Scheme 77

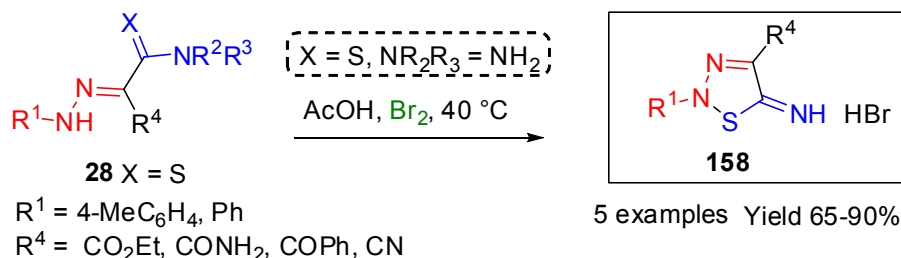
4.4.5 Intramolecular cyclization reactions. Intramolecular transamidation took place when 6-methoxy-2-(2-phenylhydrazono)-2*H*-chromene-3-carboxamide **22** was heated in boiling DMF with acetic anhydride for 3 h to form 6-methoxychromeno[2,3-*c*]pyrazol-3(2*H*)-one **150** (Scheme 78). It was concluded that the presence of acetic anhydride assisted the lactamisation reaction. Applying acetic acid as a reaction medium under microwave irradiation at 190 °C for 5 min led to full conversion of the starting hydrazone **22** into the desired compounds **150** with a small amount of by-product **151** in the final reaction mixture.¹⁴ It is interesting to note that heating of hydrazones **22** with acetic anhydride at reflux leads mainly to the product of double acylation (**151**) with an impurity of pyrazolone **150**.



Scheme 78

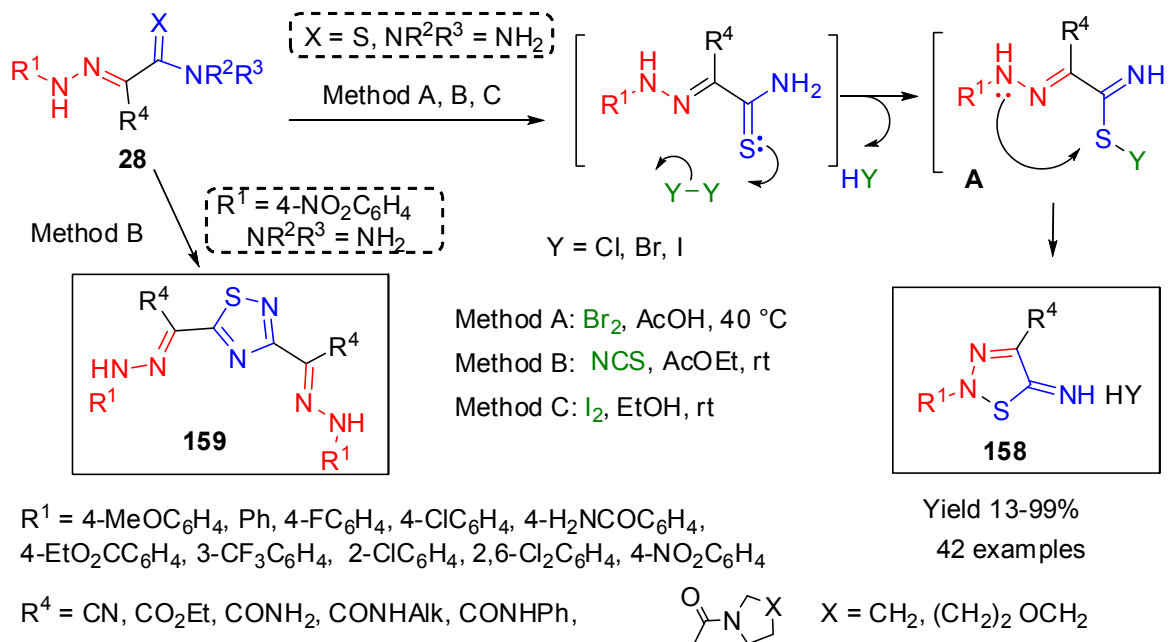
It is worth noting that highly electrophilic cyano- and keto groups located at position 4 often take part in a step of the heterocyclization process of hydrazones as shown in the Schemes 64,

4.4.7 Oxidative cyclization reactions. In this part, the literature on oxidative cyclization of hydrazones with thiocarbamoyl and amidine groups is summarized. The dehydrative cyclization reaction of 2-arylhydrazonothioacetamides **28** ($X=S$) leading to 2-aryl-2,5-dihydro-1,2,3-thiadiazole **158** was first described by Gewald and Hain for a number of derivatives of **158** (Scheme 82).^{16j,k}



Scheme 82

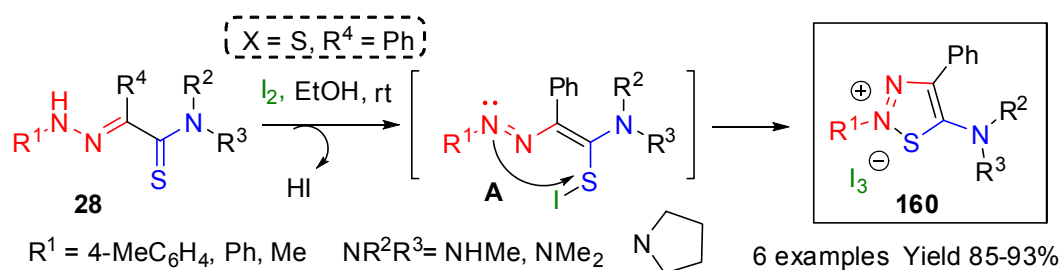
We have expanded this method, involving a large series of starting thioamido-hydrazones **28** ($X=S$) and using a number of oxidation reagents. The scope and limitations of the reaction were also determined.^{25b} In all cases, the oxidation of arylhydrazonothioacetamides with bromine in acetic acid afforded 5-imino-2,5-dihydro-1,2,3-thiadiazole salts **158** as the major products (Scheme 83).



Scheme 83

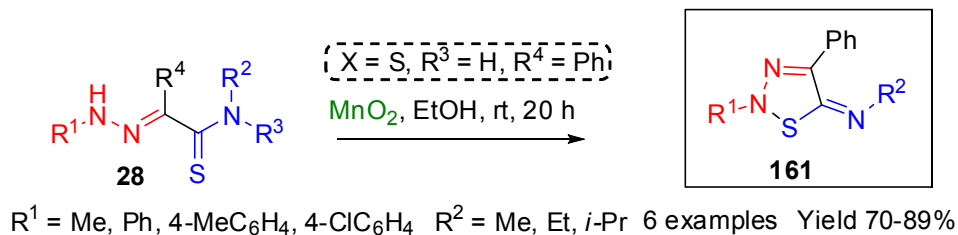
This process is characterized by good yields, with exception for the starting materials with a strong electron-acceptor substituent on the aromatic ring (CF_3 , NO_2). The oxidation of 4-nitrophenylhydrazonothioacetamide **28** ($\text{X}=\text{S}$, $\text{R}^1=4\text{-NO}_2\text{C}_6\text{H}_4$) with NCS afforded 1,2,4-thiadiazoles **159** as the only cyclic product (Scheme 83).

The oxidative dehydration of arylhydrazonothioacetamides **28** ($\text{X}=\text{S}$) by iodine was used to prepare 5-iminosubstituted-1,2,3-thiadiazolium salts of type **160** (Scheme 84).^{11a-c}



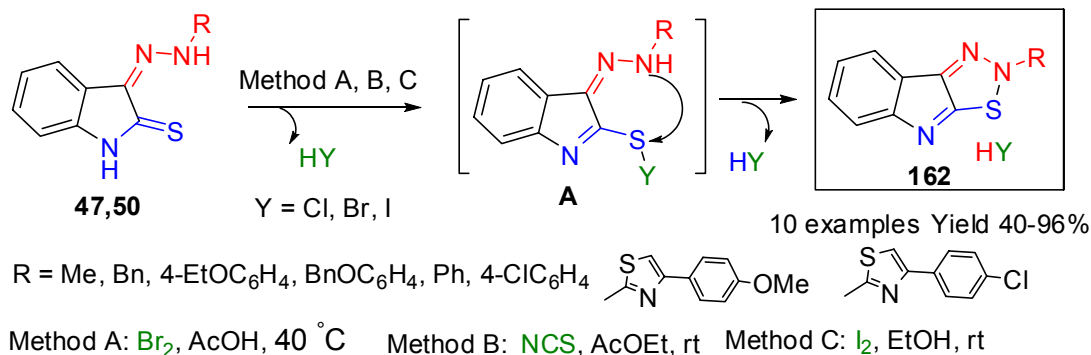
Scheme 84

N-Monosubstituted thioacetamides **28** ($\text{X}=\text{S}$, $\text{R}^3=\text{H}$) can be also oxidized with the mild oxidant manganese dioxide. The 5-imino substituted-2,5-dihydro-1,2,3-thiadiazoles **161** prepared are shown to be stable even as free bases (Scheme 85).^{11b}



Scheme 85

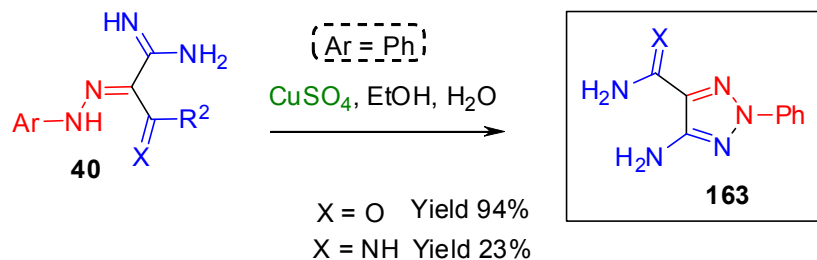
A systematic study of the oxidative cyclization of 3-hydrazono-1,3-dihydroindole-2-thiones **47**, **50** has been carried out and a series of novel 2H-[1,2,3]-thiadiazolo[5,4-*b*]-indoles **162** were obtained.²¹



Scheme 86

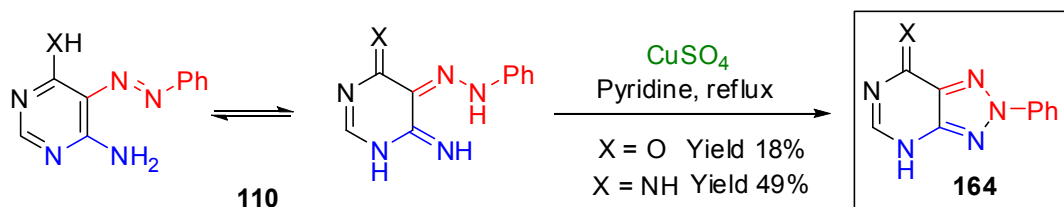
The successful synthesis of heterocycles **162** demonstrated that the oxidative cyclization of hydrazonothiocarbonyl compounds can be used for the synthesis of 1,2,3-thiadiazoles fused with other heterocyclic rings.

The oxidative cyclization of hydrazones bearing an amidine group was first initiated within a program to prepare 2*H*-1,2,3-triazol-4-amine **163** as precursors of aza-analogs of hypoxanthine and adenine, potent inhibitors of biological systems.^{23d} Thus, phenylazomalonamidine hydrochlorides **40** were converted smoothly by oxidation with copper sulfate to 4-amino-1,2,3-triazole **163** (Scheme 87).



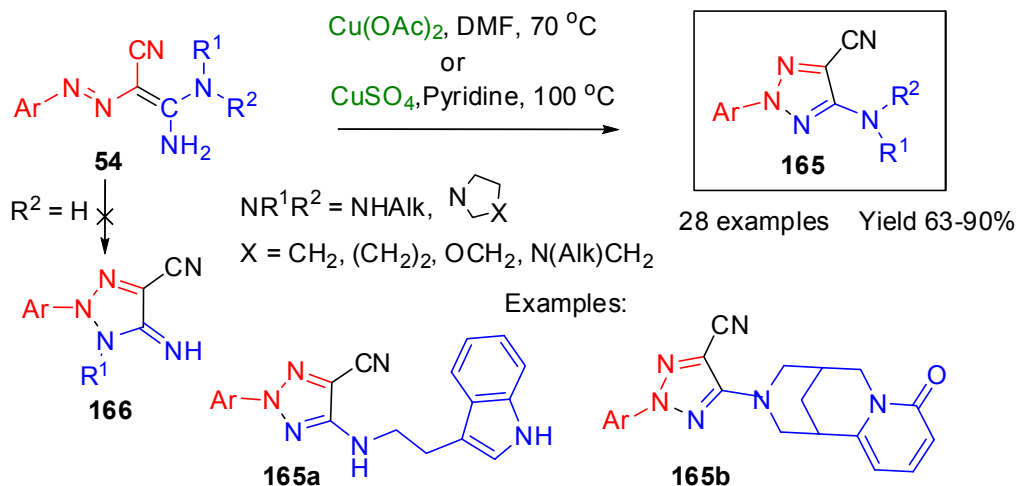
Scheme 87

Hydrazones **110** containing an amidine group can be oxidized with copper sulfate in pyridine to 2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines **164** in moderate yields (Scheme 88).^{23c}



Scheme 88

2-Arylhydrazono-N,N-dialkyl-acetamides **54** undergo cyclizations by treatment with copper sulfate in pyridine to form only the 5-dialkylamino-2-aryl-1,2,3-triazole-4-carbonitriles **165**, but not triazoles **166** (Scheme 89).^{24,27}



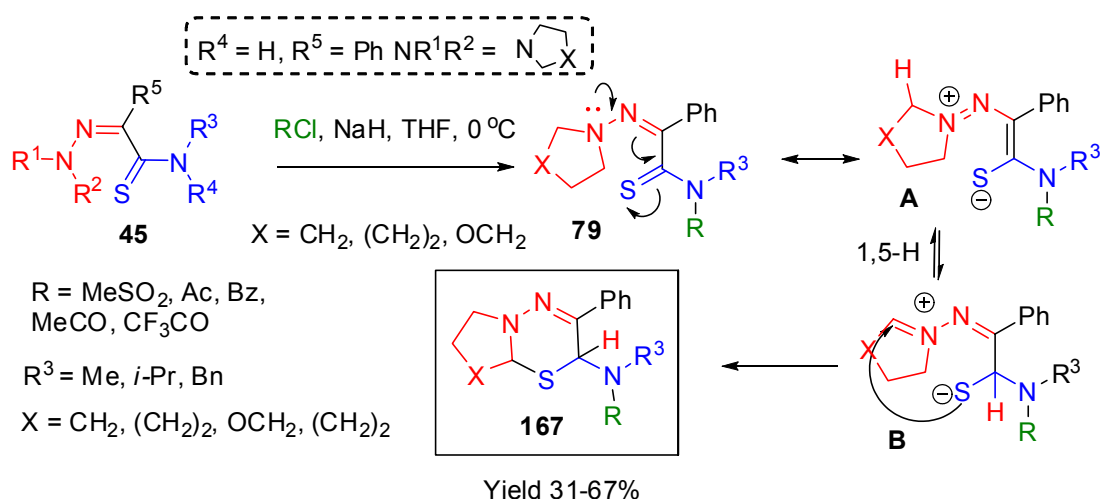
Scheme 89

It should be noted that in all cases the involvement of the primary rather than the secondary amino group in the oxidative cyclization process is observed. The scale of the present investigation shows that this reaction is a general method for the synthesis of a large variety 2-aryl-2H-1,2,3-triazole-5-amines. Furthermore, this allowed to prepare compounds **165a** and **165b** with natural product moieties, e.g. tryptamine and the alkaloid cytosine.

5. Hydrazono-thioamides for the synthesis of substrates for pericyclic transformations

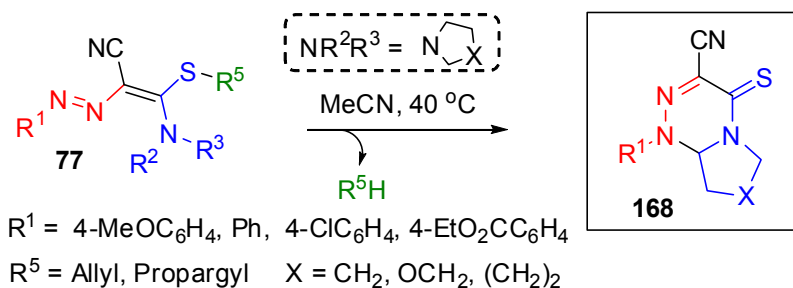
Due to the presence of electron lone pairs, the π -conjugated system and the mobility of some of their protons, arylhydrazones are often used as starting materials in the synthesis of active substrates for cycloaddition reactions.^{6,7}

Gil *et al.* have found that reaction of arylhydrazonothioacetamides with acid chlorides or mesyl chloride in the presence of sodium hydride took place at the nitrogen atom of the thioamide group to form disubstituted thioamides **79** (Scheme 90).^{11c} In most cases compounds **79** are not isolated and undergo intramolecular cyclisation to give 6-acylamino-3,6-dihydro-2H-1,3,4-thiadiazines **167**. This reaction passes probably through the zwitterionic form **A** which isomerizes to a tautomer **B** via 1,5-sigmatropic shift of hydrogen atom. In the latter the thiolate adds to the iminium carbon atom to form the final product (Scheme 90).



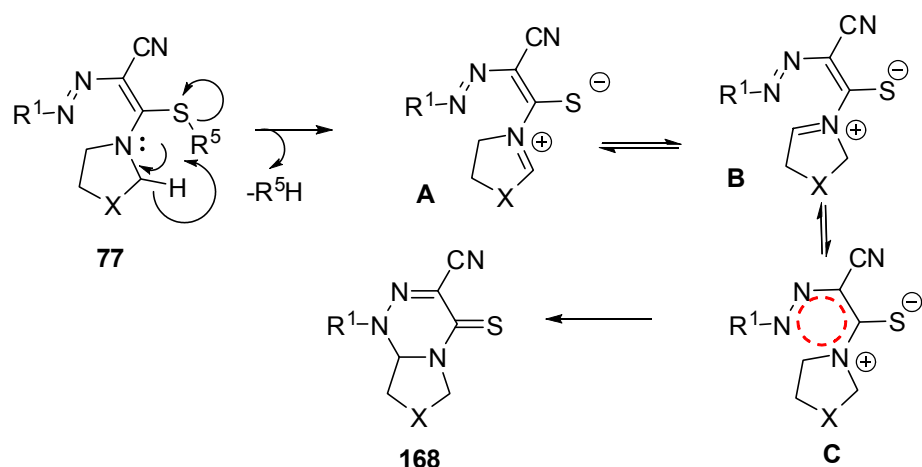
Scheme 90

We have found that 1,2-diazadienes **77**, bearing an S,N-acetal group, that were obtained by the reaction of arylhydrazonoacetothioamides **28** ($X=S$) with haloalkanes (Scheme 43) take part in various pericyclic transformations.²⁶ It has been shown that on standing in $CHCl_3$, benzene, acetone and acetonitrile at room or high temperature compounds **77** were gradually transformed into fused 1,2,4-triazines **168** as the main products in moderate yields.^{26a} (Scheme 91).



Scheme 91

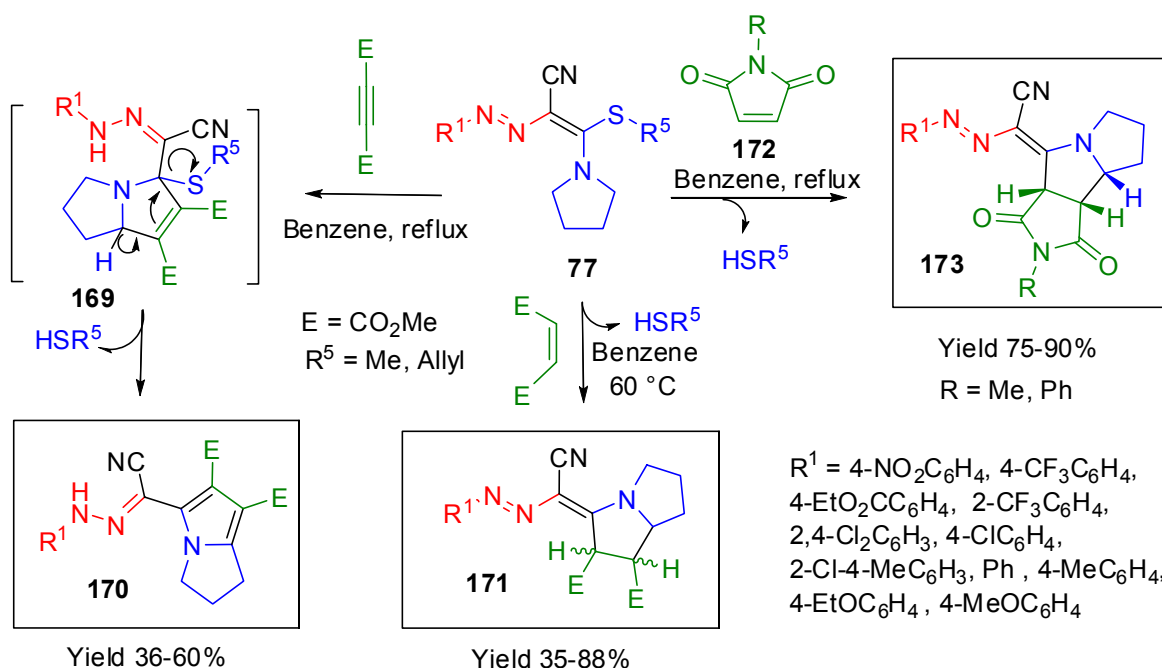
Two mechanistic possibilities for the transformation of 3-allyl- and 3-prop-1-ynylsulfanyl-2-aryldiazo-3-cycloalkylaminoacrylonitriles **77** to fused 1,2,4-triazines **168** were discussed. The first one can be described in analogy to cyclizations relying on the so called “*tert*-amino-effect” as compounds **77** contain both *tert*-amino function and a conjugated system.⁵¹ An alternative mechanism depicted in Scheme 92 involves the elimination of R^5H (propene in the case of allylthioimides **77**) to afford intermediate **A**, containing a conjugated hetero-hexatriene system. The latter undergoes a 6π -electrocyclic reaction to furnish the final product.



Scheme 92

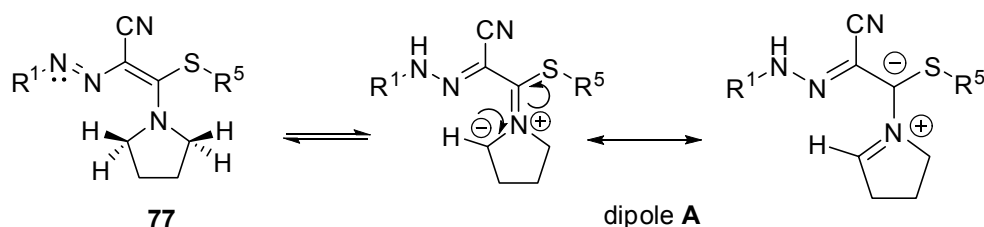
The presence of allyl(propargyl)thio group along with active α -protons makes the compounds **77** well suited for the pericyclic group transfer reactions leading to final products **168** by elimination of propene(propyne) *via* intermediate **A**. It is worth noting that the formation of propene as the principal gas-phase product of the reaction for **77** ($\text{R}^5 = \text{Allyl}$) was confirmed by a GC-MS experiment.

Interestingly, another type of pericyclic reaction occurred when 3-alkylsulfanyl-3-pyrrolidin-1-yl-2-arylazo-acrylonitrile **77** was treated with compounds that bear active triple and double bonds.^{26b,c} Thus, the reaction of compound **77** with DMAD is accomplished with elimination of alkylthiols to give the product of [3+2] addition, bicyclic pyrrole **170**. Reactions with dimethyl maleate take place in a similar way to give the mixture of isomeric pyrrolizines **171**. Compounds **173** containing three nonaromatic rings were prepared by treatment of N,S-thioacetals **77** with maleimides **172** in similar conditions (Scheme 93).



Scheme 93

The formation of these compounds was explained by a 1,3-dipolar cycloaddition of an *in situ* generated azomethine ylides. Experimental and theoretical investigation of the mechanisms of these reactions by DFT calculations allowed one to conclude that although the azo group is not included into the cyclic products it affects the mechanism of the generation of the azomethine ylides. The first step is a 1,6-hydrogen shift occurring in compounds **77** yielding the intermediate **A** (Scheme 94). The process depends on the type of the structural fragments on the sulfur and at the aromatic ring.

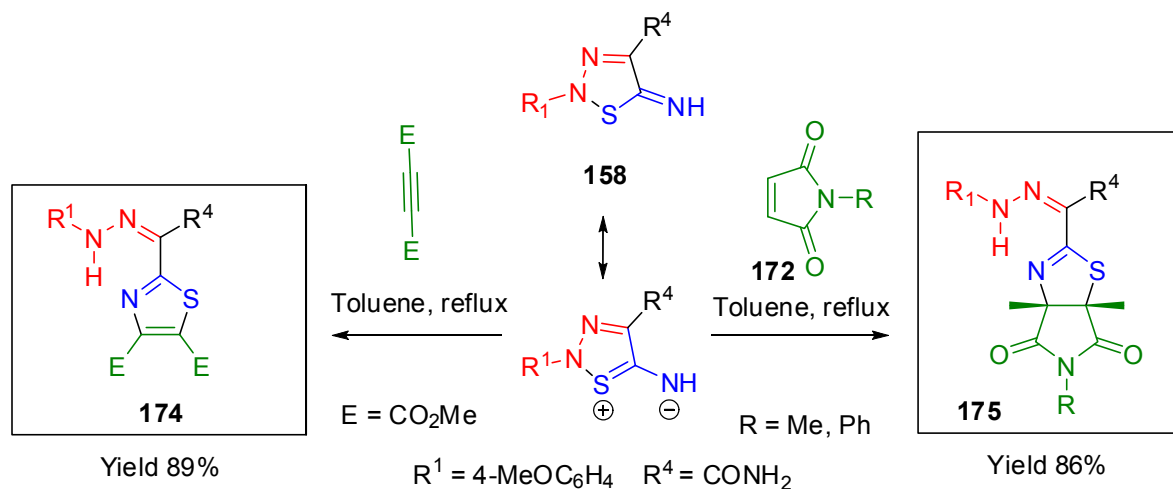


Scheme 94

Indeed, 3-alkylsulfanyl-2-arylo-3-(pyrrolidin-1-yl)acrylonitriles **77** are shown to be masked azomethine ylides that react with dipolarophiles *via* a 1,3-dipolar cycloaddition mechanism.

We have discovered that 5-imino-1,2,3-thiadiazoles **158** that were prepared from hydrazono-thioamides **28** (X=S) (Scheme 83), are also masked 1,3-dipoles and react with alkynes and

activated alkenes to form the product of 3+2 addition. Thus treatment of imines **168** with DMAD and maleimides in toluene at reflux affords monocyclic and bicyclic products **174** and **175**, respectively (Scheme 95).⁵²



Scheme 95

Conclusions

The introduction of amide, thioamide and amidine groups containing nucleophilic and electrophilic centers, electron lone pairs, mobile bonds C-heteroatom leads to new structural features and novel chemical reactions of hydrazones. The presence of several nucleophilic centers causes the hydrazones to react with various bielectrophilic reagents affording a variety of heterocyclic compounds. The presence of electrophilic centers leads to an increase of the possibilities for heterocyclizations. Both factors are the background to the use of functionalized hydrazones in the synthesis of heterocyclic compounds and for the preparations of substrates for the pericyclic reaction.

Acknowledgements

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Authors' biographies

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Belskaya Nataliya obtained her undergraduate chemistry degree in 1978 and her Ph.D in organic chemistry in 1988 from the Urals Technical Institute, Faculty of Chemistry Technology, Ekaterinburg, Russia. She was a Junior Researcher, Senior Researcher, and since 2005 she is currently associate professor at the Department of Technology for Organic Synthesis of the Urals State Technical University. Her research is focused on the chemistry of heterocyclic compounds, aromatic and heterocyclic diazo compounds, hydrazones, diazodienes, nitrilimines, nitrilylides and pericyclic reactions.

Dr Wim Dehaen Biography



Wim Dehaen was born in Kortrijk, Belgium. He obtained his Ph D in 1988 under the guidance of Professor Gerrit L'abbé on a study concerning the rearrangements of 5-diazoalkyl-1,2,3-triazole derivatives. After postdoctoral stays in Israel (1988-1990), Denmark (3 months in 1990), the United Kingdom (three months in 1994) and Belgium (most of 1990-1998) he was appointed associate professor at the University of Leuven (Belgium) in 1998, becoming a full professor at the same university in 2004. Up to 2010, close to 300 publications have appeared in international journals about his work on heterocyclic and supramolecular chemistry.

Dr Vasiliy A. Bakulev Biography

Vasiliy Bakulev was born in Ekaterinburg, Russia. He obtained PhD in 1979 under guidance of Professor Vladimir Mokrushin on the synthesis of imidazole derivatives. Then he was studding electrocyclic reactions of diazocompounds and azomethyneylides and defended in 1990 the second thesis of Doctor of Science (similar to Habilitation Work) at Moscow State University. He received a diploma of Professor in 1998. He jointly with Wim Dehaen published a book on chemistry of 1, 2, 3-thiadiazoles in 2004 and two chapters in Comprehensive Heterocyclic Chemistry III. He is currently employed as Chief of Organic Synthesis and Technology Department of the Urals State Technical University (Ekaterinburg, Russia).